DOCKET

SUPREME COURT
OF THE UNITED STATES

No. 12-398	
Title:	Association for Molecular Pathology, et al., Petitioners v. Myriad Genetics, Inc., et al.
Docketed:	October 1, 2012
Lower Ct:	United States Court of Appeals for the Federal Circuit
Case Nos.:	(2010-1406)
Decision Date:	August 16, 2012
Questions Presented	

---Date---	-------Proceedings and Orders---------------------
Sep 25 2012	Petition for a writ of certiorari filed. (Response due October 31, 2012)
Oct 3 2012	Consent to the filing of amicus curiae briefs, in support of either party or of neither party, received from counsel for the petitioners.
Oct 24 2012	Brief amici curiae of National Women's Health Network, et al filed.
Oct 26 2012	Brief amicus curiae of Academics in Law, Medicine, Health Policy and Clinical Genetics filed.
Oct 30 2012	Brief amicus curiae of AARP filed.
Oct 30 2012	Brief amici curiae of Cancer Council Australia, et al. filed.
Oct 31 2012	Brief of respondents Myriad Genetics, Inc., et al. in opposition filed.
Oct 31 2012	Brief amici curiae of Kali N. Murray and Erika R. George filed.
Oct 31 2012	Brief amici curiae of Canavan Foundation, et al. filed.
Oct 31 2012	Brief amici curiae of American Medical Association, et al. filed.
Nov 9 2012	Reply of petitioners Association for Molecular Pathology, et al. filed.
Nov 13 2012	DISTRIBUTED for Conference of November 30, 2012.
Nov 30 2012	Petition GRANTED limited to Question 1 presented by the petition.
Jan 2 2013	Consent to the filing of amicus curiae briefs, in support of either party or of neither party, received from counsel for the petitioners.
Jan 3 2013	The time to file the joint appendix and petitioners' brief on the merits is extended to and including January 24, 2013.
Jan 3 2013	The time to file respondents' brief on the merits is extended to and including March 7, 2013.
Jan 24 2013	Joint appendix filed. (2 volumes) (Statement of costs received)
Jan 24 2013	Brief of petitioners Association for Molecular Pathology, et al. filed.
Jan 28 2013	Brief amicus curiae of Juhasz Law Firm, P.C. in support of neither party filed.
Jan 29 2013	Brief amici curiae of American Medical Association, et al. filed.

Jan 30 2013	Brief amici curiae of GeneDx and Law Professors filed.
Jan 30 2013	Brief amici curiae of National Women's Health Network, et al. filed.
Jan 30 2013	Brief amicus curiae of Federation Internationale Des Conseils En Propriete Intellectuelle in support of neither party filed.
Jan 30 2013	Brief amici curiae of Academics in Law, Medicine, Health Policy and Clinical Genetics in support of neither party filed.
Jan 31 2013	Brief amicus curiae of CLS Bank International in support of neither party filed.
Jan 31 2013	Brief amicus curiae of United States in support of neither party filed.
Jan 31 2013	Brief amici curiae of International Center for Technology Assessment, et al. filed.
Jan 31 2013	Brief amicus curiae of Genformatic LLC filed.
Jan 31 2013	Brief amicus curiae of James D. Watson, Ph.D. in support of neither party filed.
Jan 31 2013	Brief amici curiae of Fifteen Law professors filed.
Jan 31 2013	Brief amicus curiae of Sigram Schindler Beteiligungsgesellschaft mbH in support of neither party filed.
Jan 31 2013	Brief amicus curiae of AARP filed.
Jan 31 2013	Brief amici curiae of Kali N. Murray and Erika R. George filed.
Jan 31 2013	Brief amicus curiae of Institute of Professional Representatives Before the European Patent Office (EPI) in support of neither party filed.
Jan 31 2013	Brief amici curiae of Ethics & Religious Liberty Commission of the Southern Baptist Convention and Prof. D. Brian Scarnecchia filed.
Jan 31 2013	Brief amicus curiae of Eric S. Lander in support of neither party filed.
Jan 31 2013	Brief amicus curiae of American Intellectual Property Law Association in support of neither party filed.
Jan 31 2013	Brief amici curiae of Canavan Foundation, et al. filed.
Jan 31 2013	Brief amicus curiae of Professor Eileen M. Kane filed.
Jan 31 2013	Brief amicus curiae of Knowledge Ecology International filed.
Jan 31 2013	Brief amicus curiae of InVitae Corporation filed.
Feb 11 2013	SET FOR ARGUMENT ON Monday, April 15, 2013
Feb 14 2013	CIRCULATED
Mar 7 2013	Brief of respondents Myriad Genetics, Inc., et al. filed. (Distributed)
Mar 13 2013	Brief amici curiae of Animal Health Institute and Merial Limited filed. (Distributed)
Mar 13 2013	Brief amicus curiae of Philadelphia Intellectual Property Law Association filed. (Distributed)
Mar 13 2013	Motion of the Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument filed.
Mar 13 2013	Record received from U.S.C.A. for Federal Circuit. (3 boxes)
Mar 14 2013	Brief amici curiae of Association of American Physicians & Surgeons, et al. filed. (Distributed)
Mar 14 2013	Brief amicus curiae of Federal Circuit Bar Association filed. (Distributed)
Mar 14 2013	Brief amicus curiae of NanoBusiness Commercialization Association filed. (Distributed)
Mar 14 2013	Brief amici curiae of Genetech, Inc., et al. filed. (Distributed)
Mar 14 2013	Brief amicus curiae of CropLife International filed. (Distributed)

Mar 14 2013	Brief amicus curiae of Coalition for 21st Century Medicine filed. (Distributed)
Mar 14 2013	Brief amicus curiae of Target Discovery, Inc. filed. (Distributed)
Mar 14 2013	Brief amicus curiae of Boston Patent Law Association filed. (Distributed)
Mar 14 2013	Brief amicus curiae of Immatics Biotechnologies, GmbH filed. (Distributed)
Mar 14 2013	Brief amicus curiae of National Venture Capital Association filed. (Distributed)
Mar 14 2013	Brief amicus curiae of Dr. Ananda Mohan Chakrabarty filed. (Distributed)
Mar 14 2013	Brief amici curiae of University of Baltimore/Johns Hopkins University Center for Medicine & Law, et al. filed.
Mar 14 2013	Brief amicus curiae of MPEG LA, LLC filed. (Distributed)
Mar 14 2013	Brief amicus curiae of New York Intellectual Property Law Association filed. (Distributed)
Mar 14 2013	Brief amicus curiae of American Bar Association filed. (Distributed)
Mar 14 2013	Brief amicus curiae of Intellectual Property Amicus Brief Clinic of the Franklin Pierce Center for Intellectual Property filed. (Distributed)
Mar 14 2013	Brief amicus curiae of Professor Jeffrey A. Lefstin filed. (Distributed)
Mar 14 2013	Brief amicus curiae of Lynch Syndrome International filed. (Distributed)
Mar 14 2013	Brief amicus curiae of Intellectual Property Owners Association filed. (Distributed)
Mar 14 2013	Brief amicus curiae of Pharmaceutical Research and Manufacturers of America filed. (Distributed)
Mar 14 2013	Brief amici curiae of Drs. Larry Geier, William Harb, Adam Ofer, and Donald Aptekar filed. (Distributed)
Mar 14 2013	Brief amicus curiae of InHouse Patent Counsel, LLC filed. (Distributed)
Mar 14 2013	Brief amici curiae of Gilead Sciences, Inc., et al. filed. (Distributed)
Mar 14 2013	Brief amicus curiae of Biotechnology Industry Organization filed. (Distributed)
Mar 15 2013	Response of respondents' to motion of the Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument filed.
Mar 18 2013	Response of petitioners' to motion of the Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument filed.
Apr 1 2013	Motion of the Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument GRANTED, and the time is to be divided as follows: 25 minutes for petitioners, 10 minutes for the Solicitor General, and 30 minutes for respondents.
Apr 2 2013	Reply of petitioners Association for Molecular Pathology, et al. filed. (Distributed)
Apr 5 2013	Record from U.S.D.C. for Southern District of New York is electronic.
Apr 15 2013	Argued. For petitioners: Christopher A. Hansen, New York, N. Y. For United States, as amicus curiae: Donald B. Verrilli, Jr., Solicitor General, Department of Justice, Washington, D. C. For respondents: Gregory A. Castanias, Washington, D. C.

PETITION FOR WRIT OF CERTIORARI

12 No. 398

Supreme Court, U.S.
FILED

SEP 2 5 2012

OFFICE OF THE CLERK
SUPREME COURT

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,

Petitioners,

—v.—

MYRIAD GENETICS, INC., ET AL.,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES
COURT OF APPEALS FOR THE FEDERAL CIRCUIT

PETITION FOR A WRIT OF CERTIORARI

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QUESTIONS PRESENTED

Many patients seek genetic testing to see if they have mutations in their genes that are associated with a significantly increased risk of breast or ovarian cancer. Respondent Myriad Genetics obtained patents on two human genes that correlate to this risk, known as BRCA1 and BRCA2. These patents claim every naturally-occurring version of those genes, including mutations, on the theory that Myriad invented something patent-eligible simply by removing ("isolating") the genes from the body. Petitioners are primarily medical professionals who regularly use routine, conventional genetic testing methods to examine genes, but are prohibited from examining the human genes that Myriad claims to own. This case therefore presents the following questions:

1. Are human genes patentable?

2. Did the court of appeals err in upholding a method claim by Myriad that is irreconcilable with this Court's ruling in *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012)?

3. Did the court of appeals err in adopting a new and inflexible rule, contrary to normal standing rules and this Court's decision in *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118 (2007), that petitioners who have been indisputably deterred by Myriad's "active enforcement" of its patent rights nonetheless lack standing to challenge those patents absent evidence that they have been personally threatened with an infringement action?

PARTIES TO THE PROCEEDINGS

The petitioners are the Association for Molecular Pathology, American College of Medical Genetics and Genomics, American Society for Clinical Pathology, College of American Pathologists, Haig Kazazian, MD, Arupa Ganguly, PhD, Wendy Chung, MD, PhD. Harry Ostrer, MD, David Ledbetter, PhD, Stephen Warren, PhD, Ellen Matloff, M.S., Elsa Reich, M.S., Breast Cancer Action, Boston Women's Health Book Collective, Lisbeth Ceriani, Runi Limary, Genae Girard, Patrice Fortune, Vicky Thomason, and Kathleen Raker. The respondents are Myriad Genetics, Inc., and in their official capacity as directors of the University of Utah Research Foundation, Lorris Betz, Roger Boyer, Jack Brittain, Arnold B. Combe, Raymond Gesteland, James U. Jensen, John Kendall Morris, Thomas Parks, David W. Pershing, and Michael K. Young. The United States Patent and Trademark Office (PTO) was dismissed as a defendant by the district court and that ruling was not appealed. Accordingly, the PTO is not a respondent here.

RULE 29.6 CORPORATE DISCLOSURE STATEMENT

Petitioners do not have any parent corporations, and no publicly held company owns 10 percent or more of the stock of any petitioner.

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Hilmi Ozcelik et al., *Long-Range PCR and Next-Generation Sequencing of BRCA1 and BRCA2 in Breast Cancer*, 14 J. Molecular Diagnostics 419, 467 (2012) 26

Tom Walsh et al., *Mutations in 12 Genes for Inherited Ovarian, Fallopian Tube, and Peritoneal Carcinoma Identified by Massively Parallel Sequencing*, 108 Proc. Nat'l Acad. Sci. U.S. 17857, 18032 (2011) 26

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OPINIONS BELOW

This Court's order granting certiorari, vacating, and remanding in light of *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* is reported at 132 S. Ct. 1794 (2012) (App. at 1a). The opinion of the United States Court of Appeals for the Federal Circuit following remand from this Court is reported at 2012 WL 3518509 (Fed. Cir. Aug. 16, 2012) (App. at 2a-119a). The Federal Circuit's original decision is reported at 653 F.3d 1329 (Fed. Cir. 2011) (App. at 120a-231a). The district court opinion granting summary judgment to petitioners and denying summary judgment to respondents is reported at 702 F. Supp. 2d 181 (S.D.N.Y. 2010) (App. at 232a-357a). An earlier opinion of the district court denying the motion to dismiss based, in part, on standing is reported at 669 F. Supp. 2d 365 (S.D.N.Y. 2009) (App. at 358a-425a).

JURISDICTIONAL STATEMENT

The Federal Circuit's decision in this case following remand was issued on August 16, 2012. This petition is thus timely. Jurisdiction is conferred by 28 U.S.C. § 1254(1).

STATUTORY PROVISION INVOLVED

35 U.S.C. § 101 provides: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."

STATEMENT

1. This is the second petition filed in this case. The prior petition was granted, and the case vacated and remanded for further proceedings in light of this Court's decision in *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012). Upon remand, a divided panel of the Federal Circuit reaffirmed its earlier ruling upholding the challenged composition claims and one of the method claims, after concluding that *Mayo* was largely irrelevant to the issues presented here.

2. The central issue in this case is whether human genes may be patented. More specifically, this case challenges patents awarded to Myriad Genetics on two genes, known as BRCA1 and BRCA2 because mutations of those genes correlate with an increased risk of hereditary breast and ovarian cancer. App. at 20a-21a. Myriad claims exclusive control over the genes once they have been "isolated" – that is, removed from the body and other cellular material. The patent claims include every single natural variation of the genes, including those that have not yet been isolated. *See* App. at 297a-300a.

Myriad has exercised its authority as a patent holder to prohibit standard clinical testing of the BRCA1/2 genes, to inhibit scientific research involving the genes, and to prevent patients from accessing their own genetic information. Myriad's patents have allowed it to dictate the cost of genetic testing, stopped other laboratories from creating and offering new and improved testing procedures, and made it impossible to obtain second opinions that could better inform patients of their cancer risk. Myriad and other gene patent holders have gained the right to exclude the rest of the scientific community from examining the naturally-occurring genes of every person in the United States.

3. Every human body contains DNA. Genes are fragments of DNA that uniquely embody laws of nature that determine, in part, the structure and functions of the body. App. at 257a-63a. They do so by coding for and producing proteins (or polypeptides) that do the work of the body and define many of our characteristics. *Id.* Genes are created naturally and can vary from one individual to another. App. at 260a-61a. Genetic alterations or variations, which also occur naturally, can be inherited or can occur after birth. App. at 378a. Variants can appear to be unimportant, correlate with an increased risk of disease or disorder ("mutations"), or have unknown significance ("variant of unknown significance"). App. at 261a. The significance of the variant is purely a function of nature. App. at 270a.

Certain BRCA1/2 mutations have been correlated with a much higher risk of cancer. "Women with BRCA1 and BRCA2 mutations face up to an 85% cumulative risk of breast cancer as well as an up to 50% cumulative risk of ovarian cancer . . . The existence of BRCA1 and BRCA2 mutations is therefore an important consideration in the provision of clinical care for breast and/or ovarian cancer." App. at 278a, 20a. Thus, for many patients, knowing whether their genes contain the harmful mutations is essential to making informed medical decisions. App. at 278a-79a, 20a.

In order to provide effective treatment to patients and to research a wide range of diseases, including cancer, medical professionals conduct genetic testing for clinically significant alterations. App. at 270a-72a. There are a variety of methods by which medical professionals can examine genes. *Id.* Basic methods involve "isolating" the DNA, which removes the DNA from the cell and associated material and randomly fragments it. Fed. Cir. Second Corrected App. Vol. VI at A7036-39.[1] Myriad did not develop the methods by which geneticists "isolate" the BRCA1/2 genes, App. at 270-72a, and those methods, which are routinely used by geneticists to sequence thousands of other human genes on a daily basis, *id.*, are not the subject of this lawsuit.

Standard isolation results in random DNA fragments that are identical to those that exist naturally in the body. Pls.-Appellees' Pet. for Panel Reh'g at 6-8, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 653 F.3d 1329 (Fed. Cir. 2011). Isolation simply makes a person's genetic information more accessible for sequencing by medical professionals. App. at 270a. After sequencing, the medical professional has a long string of four letters (A, C, T, and G) that correspond to the four nucleotides that make up DNA and genes. App. at 257a, 260a-61a. The structure, function, and sequence of the nucleotides are created entirely by nature. *Id.* The medical professional looks to see if there are variants, *e.g.*, whether natural processes have caused there to be a C where a T would normally be. App. at 260a-61a. The patents on the DNA give Myriad the exclusive right to look for variants of BRCA1 and BRCA2, even when using routine, conventional methods for isolating and sequencing.

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[1] Citations to the appendix filed below with the Federal Circuit are denoted Fed. Cir. App. Vol. ___ at ___.

Myriad defends its patents on the grounds that those patents cover only "isolated" genes, and that "isolated" genes are distinguishable from genes in the body. Yet, after completing its genetic tests, Myriad issues a report that essentially says: We have examined the genes obtained (or "isolated") from your blood sample. Because they are identical to the genes in your body, we can say with assurance that you do (or do not) have a variant. App. at 270a-72a, 279a. Further, based on the medical literature, this variant does (or does not) mean you have an increased risk of breast or ovarian cancer (or we do not know what the significance of the variant is). *Id.* If the "isolated" genes patented by Myriad were not identical to the genes in the body, Myriad could not use them to provide genetic information to patients.

4. This lawsuit began in 2009 with the filing of a complaint in the United States District Court for the Southern District of New York against the United States Patent and Trademark Office (PTO), as well as the patent holders, Myriad Genetics and the directors of the University of Utah Research Foundation.[2] Plaintiffs include four national organizations of physicians, geneticists, researchers, clinicians, and other health professionals with a combined total of over 150,000 members, as well as six of the nation's leading geneticists, two genetic

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[2] The University of Utah Research Foundation is an owner or co-owner of each of the challenged patents, App. at 248a, and has acted jointly with Myriad throughout the litigation.

counselors, two women's health and breast cancer organizations, and six patients who have been diagnosed with or are at risk of hereditary breast or ovarian cancer. App. at 240a-48a.

Plaintiffs alleged in their complaint that the patents are invalid under Section 101 of the Patent Act because they cover products and laws of nature and abstract ideas. They also alleged that the effect of the challenged patents is to preempt scientific inquiry and medical care to the detriment of patients' health and scientific advancement, in violation of both Article I, Section 8, Clause 8 and the First Amendment of the U.S. Constitution.

The complaint challenged fifteen claims from seven different patents. App. at 297a-303a. Nine of the challenged claims cover the BRCA1/2 genes.[3] Each of those claims defines the gene according to how it functions in the body – *i.e.*, that it codes for and produces a polypeptide or protein. App. at 297a-300a. For example, claims in the patent 5,747,282 ('282) include:

> 1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.

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[3] The complaint also challenged method claims on comparing the "wild-type" or non-mutated genetic sequence to the genetic sequence of a sample obtained from a patient. App. at 301a-302a. All but one of the method claims were declared invalid by both the district court and the Federal Circuit. App. at 63a-67a, 344a-53a. The five method claims declared invalid are not the subject of this petition.

> 2. The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1.
>
> 5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.

App. at 297a-99a. The patent specifications define "isolated" DNA as having been removed from the cell and separated from other genetic material. App. at 307a-08a. The referenced sequences (*e.g.*, SEQ ID NO.___) identify the lengthy nucleotide sequences found in a "wild-type" (non-mutated or normal) BRCA1 gene and the amino acid sequence found in a protein created by a wild-type BRCA1 gene. App. at 10a-11a. Other claims cover all variations and mutations in the BRCA1/2 genes, both known and unknown. App. at 296a-300a.[4]

Some of Myriad's claims, such as claim 5 of patent '282, explicitly cover any isolated DNA having 15 nucleotides or more. Because DNA with as few as 15 nucleotides of the BRCA1 gene appear throughout the genome, these claims extend to segments of other genes. App. at 115a-16a, 299a; Fed. Cir. App. Second Corrected App. Vol. VI at A7017. Moreover, according to the patent specifications, each of the claims covers virtually every short fragment of the BRCA1/2 genes and the full-length genes. *E.g.*, '282 patent at 6:26-30, 25:36-37. Also according to the specifications, all of the claims cover cDNA, a form of DNA that is complementary to naturally-occurring RNA in which some of the non-protein-coding nucleotides known as introns have been removed.

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[4] The other claims at issue in this petition are set forth in the Appendix. App. at 426-28a.

App. at 266a-68a, 336a-39a; *but see* App. at 47a, n.9. Myriad has never argued that any of its claims is limited to one form of DNA, including cDNA. Through its combined patents, Myriad claims ownership of the BRCA1/2 genes of every person in the United States.

In addition, this petition involves one method claim. Claim 20 of the '282 patent is on "a method for screening potential cancer therapeutics," which involves "growing a transformed eukaryotic [human or animal] cell containing an altered BRCA1 gene causing cancer in the presence of a compound suspected of being a cancer therapeutic" and then comparing the growth rate with the growth rate of the cell in the absence of the compound. App. at 12a-13a, 426a. Claim 20 patents the basic scientific process of observing the naturally-occurring growth rate of a cell with a BRCA1 mutation grown in the presence of any compound, and comparing it to the cell's growth rate without the compound; the claim does not specify any inventive steps or tools or limit the compound that is used.[5]

5. The defendants moved to dismiss in the district court largely on the grounds that plaintiffs lacked standing. App. at 392a. The court denied that motion. App. at 412a. Both plaintiffs and Myriad subsequently moved for summary judgment, and the PTO moved for judgment on the pleadings. App. at 237a. The district court granted the plaintiffs' motion for summary judgment and denied

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[5] Claim 20 is no different from a method of administering any substance to a person and observing whether the person's temperature went up or down, except that it occurs outside the body.

Myriad's motion. *Id.* The constitutional claims against the PTO were dismissed based on the doctrine of constitutional avoidance. *Id.* at 357a.

The district court's finding that each of the plaintiffs had standing was based on this Court's opinion in ***MedImmune, Inc. v. Genentech, Inc.***, 549 U.S. 118 (2007), which held that standing in patent cases should be analyzed in the same manner as in non-patent cases. The district court found that Myriad had taken affirmative acts to enforce its patents "through personal communications, cease-and-desist letters, licensing offers, and litigation." App. at 25a-26a. Each of the physician plaintiffs and at least one physician member of each of the medical association plaintiffs submitted declarations indicating they sequenced genes on a regular basis, would immediately utilize their standard sequencing methods to sequence the BRCA1/2 genes if possible, and were prevented from doing so solely as a result of fear of suit by Myriad.[6] App. at 407a-10a. The district court found that the remaining plaintiffs (genetic counselors and women's health groups who referred patients for testing, and patients who sought to be tested) had standing based on their stated desire to contribute to infringement by referring patients (or themselves) to physicians for testing, a desire frustrated solely by Myriad's active patent enforcement. App. at 410a-12a.

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[6] Drs. Kazazian and Ganguly had been sequencing BRCA1/2 genes until they were forced to stop as a result of letters and lawsuits by Myriad. App. at 21a-25a. Their declarations indicated they would consider resuming that activity if the patents were invalidated. App. at 36a.

The district court granted plaintiffs' motion for summary judgment in a 153-page, comprehensive opinion. App. at 232a-357a. The district court began by discussing the standard set by this Court for determining if a patented composition of matter – like the DNA at issue here – has been sufficiently changed so that it is no longer a law or product of nature. App. at 320a-23a (citing *Diamond v. Chakrabarty*, 447 U.S. 303 (1980); *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948); and *American Fruit Growers Inc. v. Brogdex Co.*, 283 U.S. 1 (1931)).

The district court considered Myriad's arguments regarding both structural and functional differences between "isolated" DNA and the DNA inside the human body, ultimately concluding that none caused "isolated" genes to be "markedly different," *Chakrabarty*, 447 U.S. at 310, from genes in the body. App. at 333a-44a. In holding that patents on isolated DNA claim a law and product of nature, the district court emphasized the unique properties of genes as:

> [I]nformation ... [that] reflects its primary biological function; directing the synthesis of *other* molecules in the body – namely, proteins, "biological molecules of enormous importance" which "catalyze biochemical reactions" and constitute the "major structural materials of the animal body."

App. at 335a (emphasis in original; citations omitted). The district court found that in isolating the genes, Myriad did not "alter its essential characteristic – its nucleotide sequence that is defined by nature and central to both its biological function within the cell and its utility as a research tool in the lab." App. at 342a. The court also invalidated the patents on cDNA for largely the same reason. App. at 339a.

6. Myriad appealed to the Federal Circuit. Plaintiffs did not appeal the dismissal of the PTO, which is no longer a party here, although plaintiffs continued to raise their First Amendment claims against the University of Utah defendants. The United States did, however, participate in the proceedings on the initial appeal and remand as *amicus curiae*, largely supporting plaintiffs.

A divided panel of the Federal Circuit reversed. The court was unanimous in rejecting Myriad's contention that none of the plaintiffs had standing. All three judges agreed that plaintiff Dr. Harry Ostrer had standing to sue because he had received a letter from Myriad proposing a BRCA licensing agreement for which a royalty would need to be paid and because Myriad's active patent enforcement had stopped Dr. Ostrer, and every other researcher and clinician, from performing testing. App. at 37a. The court further noted that Dr. Ostrer has "not only the resources and expertise to immediately undertake clinical BRCA testing, but also states unequivocally that he will immediately begin such testing." App. at 35a-36a. While accurate, that statement did not distinguish Dr. Ostrer from most of the other physician plaintiffs and members of the medical association plaintiffs who submitted similar or identical evidence of their resources, expertise, capability, and desire to begin testing. App. at 407a-12a. Nonetheless, the court denied the standing of other plaintiffs because, unlike Dr. Ostrer, they had not been individually contacted by Myriad, even though the court did find that Myriad had caused all similarly situated researchers to stop performing genetic testing. App. at 37a, 41a. The Federal Circuit dismissed the plaintiffs whose standing was based on contributory or inducing infringement essentially without comment. App. at 32a-33a, 41a.

Each member of the panel wrote a separate opinion discussing the patentability of human genes. Judge Lourie held that in analyzing whether an "isolated" gene has "markedly different characteristics" from what is found in nature, the functionality of the gene was irrelevant. App. at 55a. Thus, even if "isolated" genes were functionally identical to genes in the body, they would still be patentable. *Id.* He held that "isolated" DNA is structurally different from DNA on the sole basis that in the process of being removed from the body and its surrounding chemicals and tissues, a covalent (electron) bond has been broken, App. at 51a-57a, even though fragments of DNA with broken covalent bonds are created both in the body and in the "isolation" process. Pls.-Appellees' Pet. for Panel Reh'g at 4, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 653 F.3d 1329 (Fed. Cir. 2011); *see* Fed. Cir. Second Corrected App. Vol. VI at A7036-38.

Judge Moore, by contrast, found that both structure and function were relevant in determining if a composition is "markedly different" from what is found in nature. App. at 85a. She found that a full-length "isolated" gene "does not clearly have a new utility and appears to simply serve the same ends devised by nature." App. at 85a-86a. She said: "If I were deciding this case on a blank canvas, I might conclude that an isolated DNA sequence that includes most or all of a gene is not patentable subject matter." App. at 86a. She nevertheless found full-length genes to be patentable because of the "historical background" of the PTO's practice of granting gene patents and industry reliance on that practice. *Id.* Although conceding that none of the claims is limited to small fragments of genes, she nevertheless opined on their patentability. *See* App. at 82a.

In his dissenting opinion, Judge Bryson held the genes were not patentable. App. at 102a. He reasoned:

> The structural differences between the claimed "isolated" genes and the corresponding portion of the native genes are irrelevant to the claim limitations, to the functioning of the genes, and to their utility in their isolated form. The use to which the genetic material can be put, *i.e.*, determining its sequence in a clinical setting is not a new use; it is only a consequence of possession. In order to sequence an isolated gene, each gene must function in the same manner in the laboratory as it does in the human body.

App. at 110a.

7. Upon remand following *Mayo*, each panel member adhered to his or her previous views and the court again upheld the validity of Myriad's patents on DNA by the same 2-1 vote.[7]

Judge Lourie's consideration of *Mayo* was limited to two short paragraphs, which purported to distinguish *Mayo* on the ground that its reference to the preemptive effect of the invalidated patent in that case was applicable only to "laws of nature," not "products of nature." Rejecting the findings of the district court that DNA is a unique composition in its embodiment of natural laws, Judge Lourie ruled that the patents in this case do not claim a law of nature. App. at 56a. Indeed, despite *Mayo*'s explicit discussion of preemption, Judge Lourie seemingly rejected the relevance of preemption in *any* patent case by emphasizing that patents are supposed to be preemptive. App. at 58a-59a.

Judge Moore, unlike Judge Lourie, thought that *Mayo* "clearly ought to apply equally to manifestations of nature (composition claims)." App. at 79a. Even so, she did not alter her conclusion or analysis in any material way to reflect this Court's holding. Neither she nor Judge Lourie even referred to this Court's apparent rejection of her "reliance" argument in *Mayo*. 132 S. Ct. at 1305.

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[7] The court also adhered to its prior views on standing with one alteration. It found that the organizational plaintiffs did not have standing because they had not been threatened by Myriad. App. at 41a. The Federal Circuit continued to find Dr. Ostrer has standing, despite Myriad's argument that he lost standing when he moved from NYU to Montefiore Medical Center, where he is Director of Genetics and Genomic Diagnostics, App. at 25a. Dr. Ostrer submitted a declaration stating that he continues to have the desire and ability to test the BRCA1/2 genes and continues to feel threatened. *Id.*

Judge Bryson's dissenting opinion on remand applied this Court's reasoning in *Mayo*.

> Has the applicant made an 'inventive' contribution to the product of nature? Does the claimed invention involve more than "well-understood, routine, conventional" elements. Here, the answer to those questions is no.

App. at 112a. He also rejected the deference that Judge Lourie and Judge Moore had given to prior PTO practice, noting that it "give[s] the PTO lawmaking authority that Congress has not accorded it." App. at 119a.

The court's ruling on two other points was unanimous, both before and after remand. First, it held that cDNA was patentable subject matter, *e.g.*, App. at 47a-48a, 80a-81a, 98a, ignoring the district court's finding that none of the claims is limited to cDNA, that cDNA result from natural phenomena, and that cDNA sequences are found in the human genome. App. at 268a, 339a. Second, it upheld method claim 20 of patent '282,[8] stating: "By definition . . . performing operations, even known types of steps on . . . transformed subject matter" is patentable even if Myriad did not transform the subject matter and even if the "transformations" are undefined and can be routine and conventional. App. at 67a-70a.

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[8] *See* description of claim 20, p.8, *supra*.

Finally, the Federal Circuit did not address petitioners' constitutional claims, either in its original decision or on remand.

REASONS FOR GRANTING THE WRIT

I. THE QUESTION OF WHETHER HUMAN GENES AND THE INFORMATION THEY CONVEY ARE PATENTABLE SUBJECT MATTER IS OF PARAMOUNT IMPORTANCE TO THE FUTURE OF PATENT LAW, THE ADVANCEMENT OF MEDICAL SCIENCE, AND THE HEALTH OF PATIENTS.

In recent years, this Court has granted certiorari on several cases concerning the patentability of methods. *Mayo*, 132 S. Ct. 1289; *Bilski v. Kappos*, 130 S. Ct. 3218 (2010). *See also Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc., cert. dismissed*, 548 U.S. 124 (2006). Yet the Court has not addressed the patent eligibility of compositions of matter for over thirty years. It is crucial for the Court now to address that question. The results of the remand order illuminate the problem. Directed to reconsider its prior holding in light of *Mayo,* each panel member in the Federal Circuit had a different view on how, if at all, *Mayo* applied to this case.

The scientific, medical, and legal communities need guidance from this Court regarding the scope of Section 101 as it applies to compositions of matter and DNA. Four federal judges in this case have written opinions on the patentability of human genes. Each has adopted a different method of analyzing the issues. The district court judge held that neither DNA nor cDNA is patentable subject matter because the DNA that makes up genes function the same whether they are inside or outside the body. App. at 337a-44a. Circuit Judge Lourie, by contrast, held that the function of genes inside and outside the body is always irrelevant. App. at 55a. In his view, isolated DNA is patentable because removing a gene from the body necessarily alters its chemical structure. App. at 53a-58a. Judge Moore thought that the court must examine both function and structure. App. at 81a-82a. Although she found that full-length genes were functionally and to a significant degree structurally identical whether isolated or not, she nevertheless found them patentable based on patentees' reliance on PTO past practice. App. at 85a-94a. Finally, Judge Bryson found genes unpatentable because any structural changes were incidental to the isolation process and "only a consequence of possession." App. at 110a.

In reaching these various conclusions, the district court and Judge Bryson found it highly relevant that Myriad's entire business is based on the fact that "isolated" genes have the identical nucleotide sequence as genes in the body – because otherwise any diagnostic conclusions drawn from the "isolated" gene would be impossible. App. at 341a, 110a. Judges Lourie and Moore found that fact irrelevant and did not address the preemptive effect of these patents on clinical practice and research.

The Court's recent *Bilski* and *Mayo* decisions did not settle any of these disputes. The opinions of the panel members after remand each relied on the same, divided reasoning as before *Mayo*, with minimal change. Moreover, other Federal Circuit judges continue to adopt divergent views in cases raising fundamental Section 101 questions, even as to method patents. Three months after *Mayo* was issued, the Federal Circuit upheld patents on a method for exchanging financial obligations. *CLS Bank Int'l v. Alice Corp. Pty. Ltd.*, 685 F.3d 1341 (Fed. Cir. 2012). The majority ruled that Section 101 eligibility need not be decided first, as the threshold inquiry, and that unpatentability must be "manifestly evident." *See id.* at 1348, 1352. A dissent objected to the failure to identify an "inventive concept," as *Mayo* instructs. *Id.* at 1357. Federal Circuit judges have themselves recognized that "we continue to disagree vigorously over what is or is not patentable subject matter," citing to this case among others. *Compare MySpace, Inc. v. GraphOn Corp.*, 672 F.3d 1250, 1261 (Fed. Cir. 2012), *with id.* at 1269 (Mayer, J., dissenting) (stating that a "robust application of section 101 is required to ensure that the patent laws comport with their constitutionally-defined objective."). *See also Ultramercial, LLC v. Hulu, LLC*, 657 F.3d 1323, 1330 (Fed. Cir. 2011) (finding that claimed invention must be "manifestly abstract" to fall outside of Section 101), *vacated and remanded*, *WildTangent, Inc. v. Ultramerical, LLC*, 132 S. Ct. 2431 (2012); *Intervet v. Merial Ltd.*, 617 F.3d 1282, 1295 (Fed. Cir. 2010) (Dyk, J., concurring-in-part and dissenting-in-part) (voicing doubts about the Section 101 eligibility of isolated DNA).

The executive branch, too, has expressed different opinions in this litigation. The PTO granted these patents and has published guidelines authorizing patents on isolated DNA. *See* Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).[9] However, after consulting with the "Patent and Trademark Office (PTO), the National Institutes of Health (NIH), the Antitrust Division of the Department of Justice, the Centers for Disease Control and Prevention, the Office of Science and Technology Policy, and the National Economic Council, among others," the United States concluded in this case that DNA and human genes are not patentable, but that cDNA is. Br. for the United States as Amicus Curiae in Supp. of Neither Party at 1, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 653 F.3d 1329 (Fed. Cir. 2011). *See also* Br. for the United States as Amicus Curiae in Supp. of Neither Party, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 2012 WL 3518509 (Fed. Cir. Aug. 16, 2012). The PTO did not sign either brief submitted by the United States.

This case is an ideal vehicle to analyze the Section 101 question. Plaintiffs' sole claim under the Patent Act was brought pursuant to Section 101. Unlike other Federal Circuit cases dealing with isolated DNA patents, this is the first to present and thoroughly litigate the issue of whether isolated DNA is patentable subject matter. At the district court, all parties agreed on the fundamental characteristics of isolated DNA and disputed only the application of the law to the facts. App. at 254a-85a.

Until the patent eligibility of isolated genes is clarified, important stakeholders will be forced to act – or will be chilled from acting – without clear legal guidance. These include the clinicians and scientists who want to undertake testing and research involving the patented genes in order to improve diagnosis and treatment for patients. Section 101 plays an important role in invalidating patents on laws and products of nature that impede innovation, avoiding the high litigation costs and intensive resources needed to resolve, for example, novelty or obviousness inquiries. *See Mayo*, 132 S. Ct. at 1304. Thus, determining Section 101 eligibility avoids "creating significantly greater legal uncertainty," *id.*

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[9] These Guidelines are not entitled to any deference. *Arnold P'ship v. Dudas*, 362 F.3d 1338, 1340 (Fed. Cir. 2004).

There were 64 amicus briefs filed previously in the Federal Circuit and this Court, signed by 102 organizations, corporations, or individuals, all highlighting the importance of resolving this case. Among those who signed briefs supporting plaintiffs were numerous major medical associations, health care providers, and organizations committed to patient advocacy.[10] These amici weighed in because of the significant impact of gene patents on scientific advancement and health care. *See* App. at 4a-7a, 122a-26a. As the Department of Justice said in its brief to the Federal Circuit: "The extent to which basic discoveries in genetics may be patented is a question of great importance to the national economy, to medical science, and to the public health." Br. for the United States as Amicus Curiae in Supp. of Neither Party at 1, *Ass'n for Molecular*

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[10] Other amici in support of plaintiffs included the Southern Baptist Convention. A notable brief opposing gene patents was also filed by Dr. James Watson, who co-discovered DNA's double helix. Myriad's amici included associations of biotechnology corporations and patent attorneys. They too recognized that the issues raised by this petition are critical.

Pathology v. U.S. Patent and Trademark Office, 653 F.3d 1329 (Fed. Cir. 2011).[11]

Given the unresolved legal issues, the conflicting views of the PTO and the Department of Justice, and the importance of clarity for the medical and scientific communities, this case plainly merits plenary review.

II. PATENTS ON "ISOLATED" DNA ARE INVALID UNDER THIS COURT'S SECTION 101 JURISPRUDENCE AND THE U.S. CONSTITUTION.

1. The patenting of isolated DNA violates long-established Supreme Court precedent that prohibits the patenting of laws of nature, natural phenomena, products of nature, and abstract ideas. *Chakrabarty*, 447 U.S. at 309. "'[T]he relevant distinction' for purposes of § 101 is . . . 'between products of nature, whether living or not, and human-made inventions.'" *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 130, 134 (2001) (quoting *Chakrabarty*, 447 U.S. at 313). *See also Gen. Elec. Co. v. De Forest Radio Co.*, 28 F.2d 641, 643 (3d Cir. 1928); *In re Marden (Marden II)*, 47 F.2d 958, 959 (C.C.P.A. 1931); *In re Marden (Marden I)*, 47 F.2d 957, 957 (C.C.P.A. 1931). In *Mayo*, the Court affirmed that subject matter eligibility remains a threshold question, separate and distinct from considerations of utility or novelty. 132 S. Ct. at 1304.

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[11] This question will continue to impact personalized medicine, despite the achievement of the Human Genome Project, given the large number of issued patents, the ongoing approval of DNA patents, and remaining gaps in genome identification.

In upholding these patents, the Federal Circuit departed dramatically from *Mayo*, *Chakrabarty*, *Funk Brothers*, and *American Fruit Growers* – this Court's seminal cases on the law and product of nature doctrine. The Court has held that a claimed composition must have "a distinctive name, character [and] use" and "markedly different characteristics from any found in nature," *Chakrabarty*, 447 U.S. at 309-10 (alteration in original) (citation omitted); or, as *Mayo* described, what is patented must be based on an "inventive concept" and "add enough" to the natural phenomena to warrant patenting. 132 S. Ct. at 1294, 1297.

As *Mayo* makes clear, a key aspect of the Section 101 analysis turns on whether the patent preempts use of the laws and products of nature. Does the patent "risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries . . . " "relative to the contribution of the inventor?" 132 S. Ct. at 1294, 1303; *see also Funk Bros.*, 333 U.S. at 130-31 (invalidating patents that cover the "handiwork of nature" or "qualities [that] are the work of nature"). Where the claimed composition's "qualities are the work of nature," those qualities are not patentable, for "[t]hey are manifestations of laws of nature, free to all men and reserved exclusively to none." *Funk Bros.*, 333 U.S. at 130. To otherwise hold would be "allowing a patent to issue on one of the ancient secrets of nature now disclosed." *Id.* at 132. Unless the composition is rooted in an inventive concept, thus having markedly different characteristics from any found in nature, and does not tie up future innovation, the patent will encumber "the storehouse of knowledge of all men." *Id.* at 130.

The Court has examined the key characteristics of a claimed composition, including function, to determine whether they are the work of nature. Comparing the unpatentable combination of bacteria in *Funk Brothers* with the genetically-engineered and patentable *Chakrabarty* bacterium, the Court in *Chakrabarty* concluded that the latter has "markedly different characteristics from any found in nature," while the former's discovery is "nature's handiwork." *Chakrabarty*, 447 U.S. at 310 (quoting *Funk Bros.*, 333 U.S. at 131). The *Chakrabarty* bacterium was both structurally and functionally different from its natural state, containing new genetic material and becoming capable of degrading oil in its new form. By contrast, the challenged patent in *Funk Brothers* was based on a naturally-occurring phenomenon; namely, the ability of certain "isolated" bacteria to efficiently fix nitrogen without inhibiting each other. Even though the bacteria did not exist together naturally and even though their aggregate nitrogen-fixing capability had been newly identified and had commercial utility, the Court invalidated the patent because the patent holder did "not create [a] state of inhibition or of non-inhibition in the bacteria." 333 U.S. at 130-31.

Similarly, in *American Fruit Growers, Inc. v. Brogdex Co.*, the Court rejected the patenting of a fruit that had been treated with mold-resistant borax, although the "complete article is not found in nature" and despite its "treatment, labor and manipulation." 283 U.S. 1, 11-12 (1931). And in *Mayo*, the Court concluded that the patents covered a law of nature – the relationship between certain metabolite levels and drug efficacy in a patient. 132 S. Ct. at 1297. Although the claims involved human intervention in administering a drug and determining metabolite levels, they monopolized this naturally-occurring relationship and thus were invalid. *Id.*

Under this precedent, the patents on isolated DNA improperly claim products and laws of nature. The claims themselves define "isolated DNA" according to a naturally-occurring functional characteristic – namely, "coding for" a naturally-occurring polypeptide. *See, e.g.*, claim 1, '282 patent, at App. 426a. The claims explicitly recognize that DNA stores and conveys specific information – as dictated by the natural order of nucleotides – that serves as the blueprint for proteins, and ultimately the cells and organs, that make up the human body. Because this blueprint is the essential characteristic of DNA and remains the same before and after isolation, "isolated" DNA does not have markedly different characteristics from any found in nature. Both are DNA, their structures are not markedly different, the protein coded for by each is the same, and their use in storing and transmitting information about a person's heredity is identical.

Moreover, the naturally-occurring coding relationship between DNA and proteins is a law of nature, unchanged by "isolating" the DNA. Other chemicals in the human body remain the same, albeit in different quantities, from person to person; DNA, on the other hand, codes for and transmits distinctive biological information. As the district court held, "DNA, and in particular the ordering of its nucleotides, therefore serves as the physical embodiment of laws of nature – those that define the construction of the human body." App. at 335a. Isolation of DNA was a well-known technique at the time these patents were sought, and continues to be a routine preparatory step for using human genes in research and clinical practice. Fed. Cir. Second Corrected App. Vol. VI at A6963, A7037. The only "inventive concept" contained within these patents is disclosure of the law of nature; *i.e.*, the fact that this DNA codes for the BRCA protein and embodies information regarding a person's heredity and susceptibility to disease.

The broad preemptive effect of these patents is further evidence that they claim laws and products of nature. The patents cover all isolated forms of the naturally-occurring genes, whether previously identified or not. The patents grant Myriad the authority to prevent all research and clinical testing of the genes, raising the same concerns about patenting a "building-block" that has troubled the Court. *See Mayo*, 132 S. Ct. at 1303. These patents tie up basic uses of the genes, "foreclose[ing] more future innovation than the underlying discovery could reasonably justify." *Id.* at 1292. Unlike patents on drugs which can be invented around by developing another drug that treats the same condition, patents on isolated DNA bar access to every person's genetic information.

Myriad has vigorously enforced its patents, impeding medical practice and innovation in numerous ways. App. at 22a-25a, 37a, 281a-95a. It has prevented clinical testing by other labs, even during a period of several years when it failed to look for all known mutations and was thus providing false negative results to some women. App. at 279a, 285a-86a. Many women, upon obtaining results from Myriad, wish to get a second opinion before they make life-changing medical decisions, such as obtaining or refraining from prophylactic surgery, but cannot obtain confirmatory testing through other labs. App. at 288a-89a. Myriad also prevents others from providing testing at a lower price, or for free, and only 130 million of America's 308 million people can currently receive insurance coverage for their testing. Fed. Cir. Second Corrected App. Vol. VI at A4703.

The patents also interfere with deepening our knowledge about these genes and breast and ovarian cancer. Currently, Myriad collects a huge amount of data on the nature and significance of variants in the BRCA1/2 genes, but refuses to share that data with the scientific community and has no obligation to collaborate with others. App. at 289a-293a. The patents impede new advances in genetic testing that can efficiently sequence the many genes now associated with breast and ovarian cancer, or indeed the entire human genome. *See, e.g.*, Hilmi Ozcelik et al., *Long-Range PCR and Next-Generation Sequencing of BRCA1 and BRCA2 in Breast Cancer*, 14 J. Molecular Diagnostics 419, 467 (2012); Tom Walsh et al., *Mutations in 12 Genes for Inherited Ovarian, Fallopian Tube, and Peritoneal Carcinoma Identified by Massively Parallel Sequencing*, 108 Proc. Nat'l Acad. Sci. U.S. 17857, 18032 (2011).

The rationale for granting a patent – the need to create economic incentives to advance science – did not apply in this case. Other researchers were also looking for the BRCA genes and had indicated that they would share their results with the scientific community. App. at 273a-77a, 289a-94a. The widespread clinical testing of other, unpatented genes and the extraordinary importance of breast and ovarian cancers make it clear that diagnostic tests resulting from the discoveries of BRCA1/2 would have been made available to the public even without the patent incentive. *See* App. at 293a-95a; Sec'y's Advisory Comm. on Genetics, Health, & Soc'y, *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests* (2010).

Finally, it is of critical importance to patient health that knowledge about these genes increase so as to advance diagnosis and treatment of breast and ovarian cancer, as well as the many other diseases associated with these genes. Because Myriad has authority to prevent research on a part of the human body[12] and to prevent development of new or better clinical tests, the consequences for women's health are enormous. This case does not question the patentability of new instruments, drugs, or methods of diagnosis or treatments. Instead, it concerns perhaps the most basic elements of biology, human genes. As the district court found: "The widespread use of gene sequence information as the foundation for biomedical research means that resolution of these issues will have far-reaching implications, not only for gene-based health care and the health of millions of women facing the specter of breast cancer, but also for the future course of biomedical research." App. at 362a.

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[12] In opposing the first petition to this Court, Myriad claimed that it has generously permitted research. This assertion is contradicted by evidence provided by researchers. *See* Fed. Cir. Second Corrected App. Vol. III at A2673-74, A2888-93, A3022-23. And more importantly, the question in this case is not whether Myriad has been a generous corporate citizen but whether patent exclusivity permits it to prevent further research on human genes.

2. The Federal Circuit in this case reached the wrong result because it asked the wrong questions. It focused on trivial changes to DNA incidental to isolation that fall far short of "markedly different characteristics from any found in nature." It failed to identify what is inventive about these claims. And, it failed to consider their preemptive effects while giving undue weight to patentees' interests.

The opinion of the court by Judge Lourie focused only on the chemical structure of DNA, disregarding its biological characteristics. App. at 55a. ("We recognize that biologists may think of molecules in terms of their uses, but genes are in fact materials having a chemical nature and, as such, are best described in patents by their structures rather than their functions."). His conclusion contradicts both the patent claim language – which claims isolated DNA coding for a specified protein, rather than DNA with defined chemical ends – and this Court's repeated admonition that patents should be evaluated according to the actual claim language, *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 373 (1996); *White v. Dunbar*, 119 U.S. 47, 52 (1886). It also ignores the Court's decisions establishing that function is a critical factor for determining whether something is patentable under Section 101. *Chakrabarty*, 447 U.S. at 310.

Under Judge Lourie's approach, any cleavage of chemical bonds would render the resulting molecule patentable even though BRCA1/2 fragments, with covalent bonds broken, naturally exist in the body. *Compare* App. at 53a *with* Pls.-Appellees' Pet. for Panel Reh'g at 4, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 653 F.3d 1329 (Fed. Cir. 2011). Such a rule has never been endorsed by this Court, or to the best of our knowledge by any court, and runs counter to this Court's pragmatic approach to applying Section 101. *Bilski*, 130 S. Ct. at 3226-27 (rejecting a rigid "machine-or-transformation" test for method claims). As in *Bilski*, the Federal Circuit again imposed an inflexible test unrooted in precedent.

Though the concurring opinion by Judge Moore discussed the structure and function of isolated DNA, it failed to take into account whether its qualities are the work of nature. *See Chakrabarty*, 447 U.S. at 309-10; *Funk Bros.*, 333 U.S. at 130. Instead, it turned to past practice of the PTO and industry reliance to uphold claims she thought "on a blank canvas" might be invalid. App. at 86a-96a.

Despite *Mayo*'s concerns about the impact of patents on innovation, the majority refused to consider how the patents preempt use of laws and products of nature, impeding clinical and scientific work. App. at 43a-44a, 58a-59a (stating that effects of the patents, such as monopolizing genetic testing and prohibiting confirmatory testing, are not relevant to the legal question and that "limited preemption is inherent in every patent"). It is true that every valid patent excludes others from using the invention. However, the central question under Section 101 is whether the patent preempts use of a law or product of nature, as these patents do. For example, a claim that includes small segments of DNA that are not limited to the patented genes, like claim 5 of patent '282, preempts researchers from working with that segment wherever it appears in the genome, foreclosing scientific inquiry far beyond what Myriad's discovery of two genes could ever justify. *See Bilski*, 130 S. Ct. at 3230-31; *Gottschalk v. Benson*, 409 U.S. 63, 71-72 (1972); *Funk Bros.*, 333 U.S. at 130. *See also Lab. Corp. of Am. Holdings*, 548 U.S. at 126-27 (Breyer, J., dissenting) ("[S]ometimes *too much* patent protection can impede rather than 'promote the Progress of Science and useful Arts.'").

The Federal Circuit further departed from precedent by concluding that Section 101 questions should be resolved in favor of patentees based on their reliance interests. App. at 61a-62a and 87a-96a. This Court unequivocally rejected that proposition in *Mayo* when it invalidated certain medical patents that the PTO had approved for many years. 132 S. Ct. at 1304-05.

Lastly, the entire panel ignored the district court's factual finding that cDNA results from natural phenomena and can appear in the body. Ignoring the fact that nature dictates the composition and order of nucleotides that make up cDNA, the Federal Circuit held that cDNA was patentable because it is more often created in a lab. App. at 54a.

3. Patents on isolated DNA also violate the First Amendment because they block scientific inquiry into the patented DNA. These patents prevent access to each person's genetic information

and deprive others from examining the BRCA1/2 genes and engaging in fundamental scientific work. It is not possible to "invent around" human genes, as one can with a true invention, like a carburetor. Because the patents grant control over a body of knowledge and over pure information, they violate the First Amendment. *Ashcroft v. Free Speech Coal.*, 535 U.S. 234, 253 (2002) ("First Amendment freedoms are most in danger when the government seeks to control thought or to justify its laws for that impermissible end. The right to think is the beginning of freedom . . . .").

III. THE METHOD CLAIM UPHELD BELOW IS INCONSISTENT WITH *MAYO* AND SHOULD HAVE BEEN REJECTED.

The Federal Circuit properly rejected all but one of Myriad's method claims. The one it upheld should have been rejected as well. The court's failure to do so reflects a misunderstanding or misapplication of *Mayo* and warrants review given the Federal Circuit's critical role in interpreting patent law.

In *Mayo*, this Court invalidated a patent on examining a human's natural reaction to a single drug. Here, claim 20 of patent '282 similarly involves examining a human (or animal) cell's natural reaction to any potential drug.[13] The Federal Circuit found *Mayo* irrelevant to the claim's validity because instead of measuring how the drug affects the body, the scientist is measuring how the drug affects a "transformed" cell. *See* App. at 68a-69a. Yet, the patent does not require that the cell be transformed by the patent holder, just as the drug in *Mayo* was not patented by Prometheus; indeed, transformed cells containing altered DNA are conventional products widely available for purchase. Nor does the claim specify the nature of the transformation. It simply assumes that such a cell is used.

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[13] *See* description of claim 20, p. 8, *supra*.

Testing the effectiveness of a potential therapeutic by comparing its effect on cell growth with the cell growth occurring without the compound is routine, conventional science. Preventing any researcher from engaging in this science to find a cancer treatment is precisely the preemptive effect that led this Court to invalidate the claim in *Mayo* and should invalidate this claim as well.

IV. BY HOLDING THAT PETITIONERS LACKED STANDING UNLESS THEY WERE PERSONALLY THREATENED BY MYRIAD, THE FEDERAL CIRCUIT IMPOSED A RIGID STANDING REQUIREMENT CONTRARY TO THIS COURT'S APPROACH IN *MEDIMMUNE*

In *MedImmune, Inc. v. Genentech, Inc.*, this Court declared that the correct standing analysis in patent cases, as in all other Article III cases, "is whether the facts alleged, under all the circumstances, show that there is a substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment." 549 U.S. 118, 127 (2007) (citation omitted); *see also Holder v. Humanitarian Law Project*, 130 S. Ct. 2705, 2717 (2010) (citing *MedImmune* in a non-patent case for the proposition that plaintiffs face a credible threat of enforcement need not await actual enforcement before bringing a lawsuit). Exalting form over substance, the Federal Circuit improperly ruled that petitioners lacked standing unless they were personally threatened by Myriad.

Even applying its erroneous standard, the Federal Circuit held that Dr. Ostrer had standing, allowing this case to proceed. App. at 32a, 40a-42a. But, inexplicably, the court held that only Dr. Ostrer has standing despite its finding that:

> Myriad's active enforcement of its patent rights forced Dr. Ostrer, *as well as every other similarly situated researcher and institution*, to cease performing the challenged *BRCA* testing services . . . . Myriad's enforcement efforts *eliminated all competition* . . . . [N]othing in the record suggests that any researcher or institution has successfully attempted to compete with Myriad, or that Myriad has in any way changed its position with regard to its patent rights.

App. at 37a (emphasis added). According to the Federal Circuit, these facts did not establish an "injury traceable to Myriad" for anyone other than Dr. Ostrer. Instead, it characterized the injury suffered by every similarly situated researcher and institution as an "attenuated, non-proximate, effect from the existence of [Myriad's] patent." App. at 41a.

It is difficult to reconcile findings that all of the plaintiffs have been "forced to cease" their actions as a result of Myriad's patent enforcement and that the effect of Myriad's actions was to "eliminate all competition" with a holding that the effect of Myriad's actions was "attenuated, non-proximate," and insufficient to create standing. Furthermore, the idea that a plaintiff cannot have standing unless a patent holder "directed any letters or other communications regarding its patents at them," App. at 24a, is contrary to numerous decisions of this Court that parties may bring challenges even if they have not been personally threatened by those who enforce the requirement they seek to challenge.

In *MedImmune,* this Court held that the Federal Circuit's prior standing rules were contrary to precedent including *Aetna Life Ins. Co. v. Haworth,* 300 U.S. 227, 239 (1937), "where jurisdiction obtained even though the very reason the insurer sought declaratory relief was that the insured had given no indication that he would file suit." 549 U.S. at 132 n.11. This holding was consistent with this Court's precedent. *See Doe v. Bolton,* 410 U.S. 179, 188 (1973); *Virginia v. Am. Booksellers Ass'n, Inc.,* 484 U.S. 383, 393 (1988). *See also Vt. Right to Life Comm., Inc. v. Sorrell,* 221 F.3d 376, 382 (2d Cir. 2000) (civil cases); *Biotech. Indus. Org. v. District of Columbia,* 496 F.3d 1362, 1370 (Fed. Cir. 2007); App. at 286a-87a.

The Federal Circuit's newly minted rule that a party does not have declaratory judgment standing unless he or she has been personally threatened by a patent holder is erroneous. It is even more restrictive than that court's prior "reasonable apprehension" test, rejected by this Court in *MedImmune.*[14] The medical organizational plaintiffs and most of the physician plaintiffs are identical for standing purposes to Dr. Ostrer, because they have the equipment, expertise and desire to engage in testing but have refrained solely as a result of Myriad's repeated suits and threats. In addition, the Federal Circuit's inflexible standing requirement led it to wrongly dismiss the plaintiffs whose standing is based on contributory or inducing infringement. *See Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1365 (Fed. Cir. 2004) (disseminating medical information and a directory of medical service providers was sufficient to trigger liability for inducing infringement).

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[14] This was not the circuit's only clear error. Although the panel found that Dr. Ostrer had standing, the court denied the standing of the organizational plaintiff American College of Medical Genetics and Genomics (ACMG), of which Dr. Ostrer is a member. App at 41a; Fed. Cir. Second Corrected App. Vol. III at A2933. The undisputed record reflects that gene patenting is germane to ACMG's purpose. App. at 241a. Pursuant to well-established law, ACMG therefore has organizational standing. *Warth v. Seldin*, 422 U.S. 490, 511 (1975). The panel also asserted that "[n]one of the plaintiffs besides Drs. Kazazian, Ganguly, and Ostrer, allege that Myriad directed any letters or other communications regarding its patents at them." App. at 24a. That is simply incorrect and contrary to the factual findings of the district court. Plaintiff Ellen Matloff's declaration makes clear that she personally was told by Myriad that she and geneticists at Yale would violate Myriad's patents if they performed tests that were not being offered by Myriad, and which she wanted to perform. App. at 383a. The court of appeals held that a plaintiff had standing if Myriad directed "any . . . communications regarding its patents at them." Even under that standard, Ms. Matloff has standing.

CONCLUSION

For the reasons stated above, the petition for certiorari should be granted.

Respectfully submitted,

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September 24, 2012

APPENDIX

Supreme Court of the United States

No. 11-725

ASSOCIATION FOR MOLECULAR PATHOLOGY,
ET AL.,

Petitioners

v.

MYRIAD GENETICS, INC., ET AL.

ON PETITION FOR WRIT OF CERTIORARI to the United States Court of Appeals for the Federal Circuit.

THIS CAUSE having been submitted on the petition for writ of certiorari and the response thereto.

ON CONSIDERATION WHEREOF, it is ordered and adjudged by this Court that the petition for writ of certiorari is granted. The judgment is vacated with costs, and the case is remanded to the United States Court of Appeals for the Federal Circuit for further consideration in light of Mayo Collaborative Services v. Prometheus Laboratories, Inc., 566 U.S. ___ (2012).

IT IS FURTHER ORDERED that the petitioners Association for Molecular Pathology, et al. recover from Myriad Genetics, Inc., et al. Three Hundred Dollars ($300.00) for costs herein expended.

March 26, 2012

Clerk's costs: $300.00

United States Court of Appeals for the Federal Circuit

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, THE AMERICAN COLLEGE OF MEDICAL GENETICS, THE AMERICAN SOCIETY FOR CLINICAL PATHOLOGY, THE COLLEGE OF AMERICAN PATHOLOGISTS, HAIG KAZAZIAN, MD, ARUPA GANGULY, PHD, WENDY CHUNG, MD, PHD, HARRY OSTRER, MD, DAVID LEDBETTER, PHD, STEPHEN WARREN, PHD, ELLEN MATLOFF, M.S., ELSA REICH, M.S., BREAST CANCER ACTION, BOSTON WOMEN'S HEALTH BOOK COLLECTIVE, LISBETH CERIANI, RUNI LIMARY, GENAE GIRARD, PATRICE FORTUNE, VICKY THOMASON, AND KATHLEEN RAKER,

Plaintiffs-Appellees,

v.

UNITED STATES PATENT AND TRADEMARK OFFICE,

Defendant,

and

MYRIAD GENETICS, INC.,

Defendant-Appellant,

and

LORRIS BETZ, ROGER BOYER, JACK BRITTAIN, ARNOLD B. COMBE, RAYMOND GESTELAND, JAMES U. JENSEN, JOHN KENDALL MORRIS, THOMAS PARKS, DAVID W. PERSHING, AND

MICHAEL K. YOUNG, IN THEIR OFFICIAL
CAPACITY AS DIRECTORS OF THE UNIVERSITY
OF UTAH RESEARCH FOUNDATION,

Defendants-Appellants.

2010-1406

Appeal from the United States District Court for the Southern District of New York in Case No. 09-CV-4515, Senior Judge Robert W. Sweet.

Decided: August 16, 2012

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Before LOURIE, BRYSON, and MOORE, *Circuit Judges.*

Opinion for the court filed by *Circuit Judge* LOURIE. Opinion concurring in part filed by *Circuit Judge* MOORE. Opinion concurring in part and dissenting in part filed by *Circuit Judge* BRYSON.

LOURIE, *Circuit Judge.*

Myriad Genetics, Inc. and the Directors of the University of Utah Research Foundation (collectively, "Myriad") appeal from the decision of the United States District Court for the Southern District of New York holding that an assortment of medical organizations, researchers, genetic counselors, and patients (collectively, "Plaintiffs") have standing under the Declaratory Judgment Act to challenge Myriad's patents. *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 669 F. Supp. 2d 365 (S.D.N.Y. 2009) ("*DJ Op.*"). Myriad also appeals from the district court's decision granting summary judgment that all of the challenged claims are drawn to non-patentable subject matter under 35 U.S.C. § 101. *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 702 F. Supp. 2d 181 (S.D.N.Y. 2010) ("*SJ Op.*"). We affirm in part and reverse in part.

This appeal has returned to us as, a petition for certiorari having been filed from our decision of July 29, 2011, the Supreme Court of the United States granted the petition, vacated our decision, and remanded the case to us for further consideration in light of its decision in *Mayo Collaborative Services v.*

Prometheus, Inc., 566 U.S. ___, 132 S. Ct. 1289 (2012). *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 132 S. Ct. 1794 (2012). We invited and received briefing by the parties and interested amici and held oral argument on July 20, 2012. Our decision on remand follows. It both decides the issues that were before us in the original appeal and evaluates the effect of *Mayo* on those issues.

On the threshold issue of jurisdiction, we affirm the district court's decision to exercise declaratory judgment jurisdiction because we conclude that at least one plaintiff, Dr. Harry Ostrer, has standing to challenge the validity of Myriad's patents. On the merits, we reverse the district court's decision that Myriad's composition claims to "isolated" DNA molecules cover patent-ineligible products of nature under § 101 because each of the claimed molecules represents a nonnaturally occurring composition of matter. We also reverse the district court's decision that Myriad's method claim to screening potential cancer therapeutics via changes in cell growth rates of transformed cells is directed to a patent-ineligible scientific principle. We affirm the court's decision, however, that Myriad's method claims directed to "comparing" or "analyzing" DNA sequences are patent ineligible; such claims include no transformative steps and cover only patent-ineligible abstract, mental steps.

BACKGROUND

Plaintiffs brought suit against Myriad, challenging the patentability of certain composition and method claims relating to human genetics. *See DJ Op.*, 669 F. Supp. 2d at 369-76. Specifically, Plaintiffs sought a declaration that fifteen claims from seven patents assigned to Myriad are drawn to patent-ineligible subject matter under 35 U.S.C. § 101: claims 1, 2, 5, 6, 7, and 20 of U.S. Patent 5,747,282 ("the '282 patent"); claims 1, 6, and 7 of U.S. Patent 5,837,492 ("the '492 patent"); claim 1 of U.S. Patent 5,693,473 ("the '473 patent"); claim 1 of U.S. Patent 5,709,999 ("the '999 patent"); claim 1 of U.S. Patent 5,710,001 ("the '001 patent"); claim 1 of U.S. Patent 5,753,441 ("the '441 patent"); and claims 1 and 2 of U.S. Patent 6,033,857 ("the '857 patent").

The challenged composition claims cover two "isolated" human genes, *BRCA1* and *BRCA2* (collectively, "*BRCA1/2*" or "*BRCA*"), and certain alterations, or mutations, in these genes associated with a predisposition to breast and ovarian cancers. Representative composition claims include claims 1, 2, and 5 of the '282 patent:

> 1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.
>
> 2. The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1.
>
> 5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.

'282 patent col.153 l.55 – col.154 l.56.[1] SEQ ID NO:2 depicts the amino acid sequence of the BRCA1 protein, and SEQ ID NO:1 depicts the nucleotide sequence of the *BRCA1* DNA coding region; the latter sequence is colloquially referred to as cDNA. *Id.* col.19 ll.48-50.

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[1] In addition to representative claims 1, 2, and 5 of the '282 patent, other claims to isolated DNA molecules at issue in this appeal include: claims 6 and 7 of the '282 patent; claims 1, 6, and 7 of the '492 patent; and claim 1 of the '473 patent.

All but one of the challenged method claims cover methods of "analyzing" or "comparing" a patient's *BRCA* sequence with the normal, or wild-type, sequence to identify the presence of cancer-predisposing mutations. Representative method claims include claims 1 of the '999 and '001 patents:

> 1. A method for detecting a germline alteration in a BRCA1 gene, said alteration selected from the group consisting of the alterations set forth in Tables 12A, 14, 18 or 19 in a human which comprises *analyzing* a sequence of a BRCA1 gene or BRCA1 RNA from a human sample or *analyzing* a sequence of BRCA1 cDNA made from mRNA from said human sample with the proviso that said germline alteration is not a deletion of 4 nucleotides corresponding to base numbers 4184-4187 of SEQ ID NO:1.

'999 patent col.161 ll.17-25 (emphases added).

> 1. A method for screening a tumor sample from a human subject for a somatic alteration in a BRCA1 gene in said tumor which comprises *comparing* a first sequence selected from the group consisting of a BRCA1 gene from said tumor sample, BRCA1 RNA from said tumor sample and BRCA1 cDNA made from mRNA from said tumor sample with a second sequence selected from the group consisting of BRCA1 gene from a

> nontumor sample of said subject, BRCA1 RNA from said nontumor sample and BRCA1 cDNA made from mRNA from said nontumor sample, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said tumor sample from the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said nontumor sample indicates a somatic alteration in the BRCA1 gene in said tumor sample.

'001 patent col.155 ll.2-17 (emphasis added).[2]

The final method claim challenged by Plaintiffs is directed to a method of screening potential cancer therapeutics. Specifically, claim 20 of the '282 patent reads as follows:

> 20. A method for screening potential cancer therapeutics which comprises: growing a *transformed eukaryotic host cell* containing an altered BRCA1 gene causing cancer in the presence of a compound suspected of being a cancer therapeutic, growing said *transformed eukaryotic host cell* in the absence of said compound, determining the rate of growth of said host cell in the presence of said compound and the rate of growth of said host cell in the absence of said compound and comparing the growth rate of said host cells, wherein a slower rate of growth of said host

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[2] The claims currently before us that recite methods of "analyzing" or "comparing" *BRCA* sequences are: claims 1 of the '999, '001, and '441 patents and claims 1 and 2 of the '857 patent.

cell in the presence of said compound is indicative of a cancer therapeutic.

'282 patent col.156 ll.13–24 (emphases added).

The challenged claims thus relate to isolated gene sequences and diagnostic methods of identifying mutations in these sequences. To place this suit in context, we take a step back to provide background on the science involved, including the identification of the *BRCA* genes, and the Plaintiffs' connections to the invention and to Myriad.

I.

Human genetics is the study of heredity in human beings.[3] The human genome, the entirety of human genetic information, contains approximately 22,000 genes, which form the basis of human inheritance. The majority of genes act by guiding the production of polypeptide chains that form proteins. Proteins in turn make up living matter and catalyze a variety of cellular processes.

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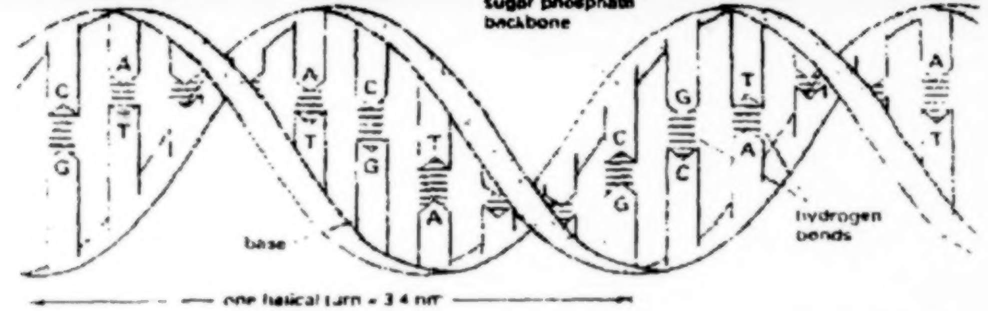
[3] The district court's opinion, *SJ Op.*, 702 F. Supp. 2d at 192-203, contains a detailed and comprehensive discussion of the science involved in this case. We repeat only the basics here.


sugar phosphate backbone
base
hydrogen bonds
one helical turn = 3.4 nm

Chemically, the human genome is composed of deoxyribonucleic acid ("DNA"). Each DNA molecule is made up of repeating units of four nucleotide bases—adenine ("A"), thymine ("T"), cytosine ("C"), and guanine ("G")—which are covalently linked, or bonded,[4] together via a sugar-phosphate, or phosphodiester, backbone. DNA generally exists as two DNA strands intertwined as a double helix in which each base on a strand pairs, or hybridizes, with a complementary base on the other strand: A pairs with T, and C with G. Figure 1 below depicts the structure of a DNA double helix and the complementary pairing of the four nucleotide bases, represented by A, T, C, and G.

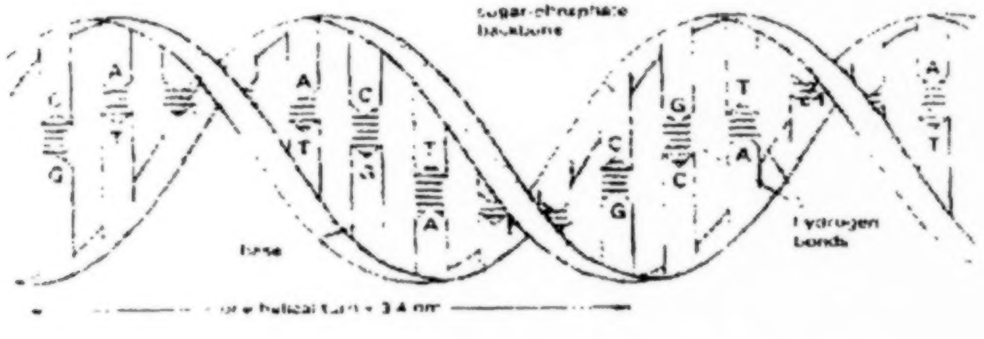

sugar-phosphate backbone
base
hydrogen bonds
one helical turn = 3.4 nm

Figure 1

The linear order of nucleotide bases in a DNA molecule is referred to as its "sequence." The sequence of a gene is thus denoted by a linear sequence of As, Ts, Gs, and Cs. "DNA sequencing" or

---

[4] Covalent bonds are chemical bonds characterized by the sharing of electrons between atoms in a molecule.

"gene sequencing" refers to the process by which the precise linear order of nucleotides in a DNA segment or gene is determined. A gene's nucleotide sequence in turn encodes for a linear sequence of amino acids that comprise the protein encoded by the gene, *e.g.*, the ***BRCA1*** gene encodes for the BRCA1 protein. Most genes have both "exon" and "intron" sequences. Exons are DNA segments that are necessary for the creation of a protein, *i.e.*, that code for a protein. Introns are segments of DNA interspersed between the exons that, unlike exons, do not code for a protein.

The creation of a protein from a gene comprises two steps: transcription and translation. First, the gene sequence is "transcribed" into a different nucleic acid called ribonucleic acid ("RNA"). RNA has a chemically different sugar-phosphate backbone than DNA, and it utilizes the nucleotide base uracil ("U") in place of thymine ("T"). During transcription, the DNA double helix is unwound and each nucleotide on the non-coding, or template, DNA strand is used to make a complementary, single-stranded RNA molecule that mirrors the coding DNA strand, *i.e.*, adenine on the template DNA strand results in uracil in the RNA molecule, thymine results in adenine, guanine in cytosine, and cytosine in guanine. The resulting "pre-RNA," like the DNA from which it was generated, contains both exon and intron sequences. Next, the introns are physically excised from the pre-RNA molecule, followed by "splicing" the exons to produce a messenger RNA ("mRNA"). Figure 2 below shows the steps of transcribing a gene that contains three exons (exon 1-3) and two introns (intron 1 and 2) into a pre-RNA, followed by RNA excising the introns and splicing of the exons to produce an mRNA containing only exon sequences.

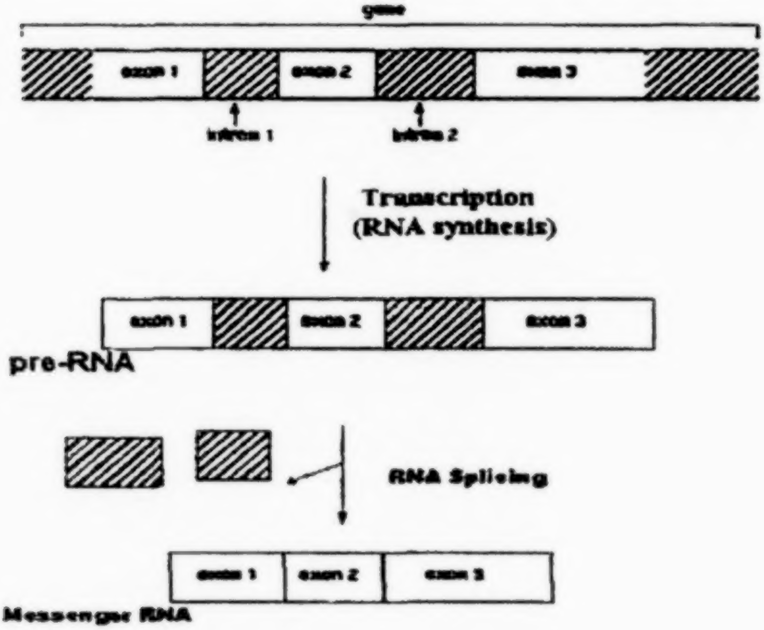

gene
exon 1
exon 2
exon 3
intron 1
intron 2
Transcription
(RNA synthesis)
exon 1
exon 2
exon 3
pre-RNA
RNA Splicing
exon 1
exon 2
exon 3
Messenger RNA

Figure 2

Following transcription and splicing, the resulting mRNA is "translated" into the encoded protein. Genes, and their corresponding mRNAs, encode proteins via three-nucleotide combinations called codons. Each codon triplet corresponds to one of the twenty amino acids that make up all proteins or a "stop" signal that terminates protein translation. For example, the codon adenine-thymine-guanine (ATG, or AUG in the corresponding mRNA), encodes the amino acid methionine. The relationship between the sixty-four possible codon sequences and their corresponding amino acids is known as the genetic code. Figure 3 below represents an mRNA molecule that translates into a protein of six amino acids (Codon 1, AUG, methionine; Codon 2, ACG, threonine; Codon 3, GAG, glutamic acid; Codon 4, CUU, leucine; Codon 5, CGG, arginine; Codon 6, AGC, serine), and ends with one of the three stop codons, UAG.

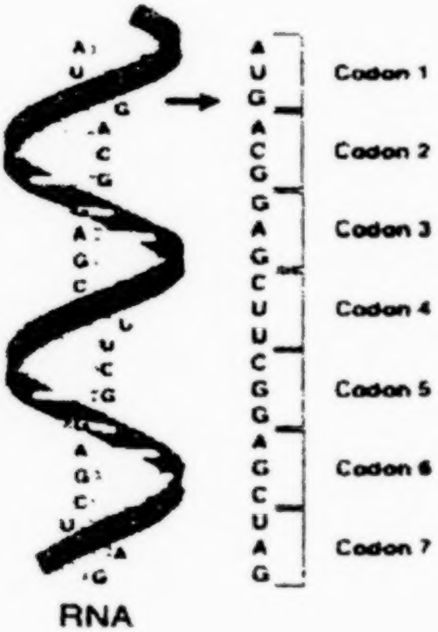

RNA
A
U
G
A
C
G
G
A
G
C
U
U
C
G
G
A
G
C
U
A
G
Codon 1
Codon 2
Codon 3
Codon 4
Codon 5
Codon 6
Codon 7

Figure 3

Changes, or mutations, in the sequence of a human gene can alter the production, structure, and/or function of the resulting protein. Small-scale changes include point mutations in which a change to a single nucleotide alters a single amino acid in the encoded protein. For example, a base change in the codon *G*CU to *C*CU changes an alanine in the encoded protein to a proline. Larger scale variations include the deletion, rearrangement, or duplication of larger DNA segments—ranging from several hundreds to over a million nucleotides—and can result in the elimination, misplacement, or duplication of an entire gene or genes. While some mutations have little or no effect on the body's processes, others result in disease or an increased risk of developing a particular disease. DNA sequencing is used in clinical diagnostic testing to determine whether a gene contains mutations associated with a particular disease or disease risk.

Nearly every cell in the human body contains an individual's entire genome. DNA in the cell, called "native" or "genomic" DNA, is packaged into twenty-three pairs of chromosomes. Chromosomes are complex structures comprising a single extended DNA molecule wrapped around proteins called histones, as shown in Figure 4 below.

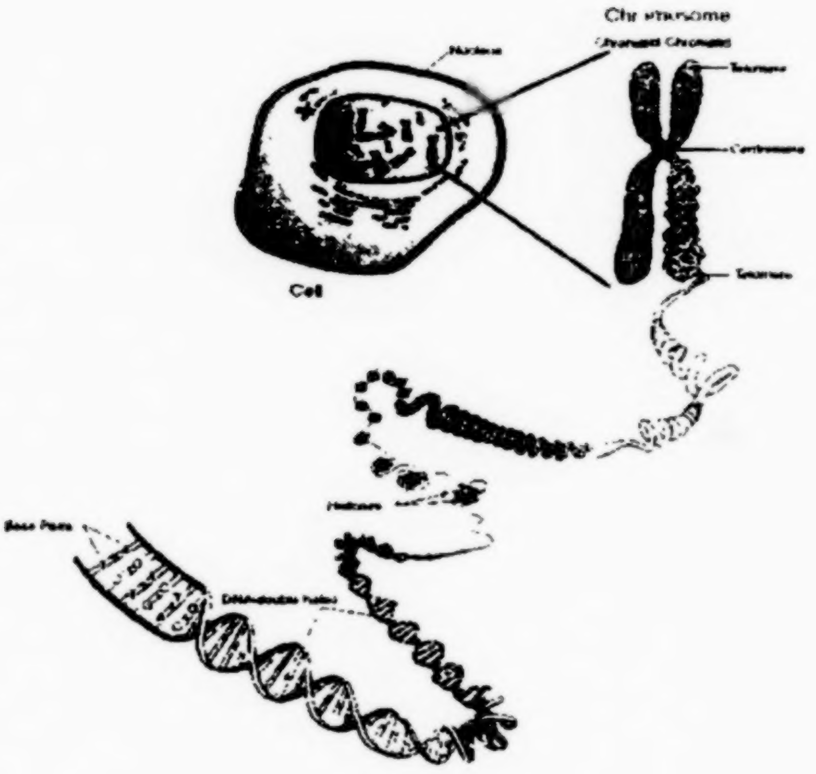


Figure 4

Each chromosome contiguously spans millions of bases and encompasses many discrete genes. Humans have twenty-two pairs of autosomal chromosomes, numbered one to twenty-two according to size from largest to smallest, and one pair of sex chromosomes, two X chromosomes in females and one X and one Y chromosome in males.

Genomic DNA can be extracted from its cellular environment using a number of well-established laboratory techniques. A particular segment of DNA, such as a gene, can then be excised or amplified from the DNA to obtain the isolated DNA segment of interest. DNA molecules can also be synthesized in the laboratory. One type of synthetic DNA molecule is complementary DNA ("cDNA"). cDNA is synthesized from mRNA using complementary base pairing in a manner analogous to RNA transcription. The process results in a double-stranded DNA molecule with a sequence corresponding to the sequence of an mRNA produced by the body. Because it is synthesized from mRNA, cDNA contains only the exon sequences, and thus none of the intron sequences, from a chromosomal gene sequence.

II.

Certain mutations in the *BRCA* genes correlate with an increased risk of breast and ovarian cancer. The average woman in the United States has around a twelve to thirteen percent risk of developing breast cancer in her lifetime. Women with *BRCA* mutations, in contrast, face a cumulative risk of between fifty to eighty percent of developing breast cancer and a cumulative risk of ovarian cancer of between twenty to fifty percent. Diagnostic genetic testing for the existence of *BRCA* mutations is therefore an important consideration in the provision of clinical care for breast or ovarian cancer. This testing provides a patient with information on her risk for hereditary breast and ovarian cancers, and thus aids in the difficult decision regarding whether to undertake preventive options, including prophylactic surgery. Diagnostic results can also be an important factor in structuring an appropriate course of cancer treatment, since certain forms of therapy are more effective in treating cancers related to *BRCA* mutations.

The inventors of the patents in suit identified the genetic basis of *BRCA1*- and *BRCA2*-related cancers "using an analysis called positional cloning. Relying on a large set of DNA samples from families with inherited breast and ovarian cancers, the inventors correlated the occurrence of cancer in individual family members with the inheritance of certain marker DNA sequences. This allowed the inventors to identify, or "map," the physical location of the *BRCA* genes within the human genome and to isolate the *BRCA* genes and determine their exact nucleotide sequences. This in turn allowed Myriad to provide *BRCA* diagnostic testing services to women.[5]

III.

Myriad, however, was not the only entity to implement clinical *BRCA* testing services. Starting in 1996, the University of Pennsylvania's Genetic Diagnostic Laboratory ("GDL"), co-directed by plaintiffs Haig H. Kazazian, Jr., M.D. and Arupa Ganguly, Ph.D., provided *BRCA1/2* diagnostic services to women. By 1999, however, accusations by Myriad that GDL's *BRCA* testing services infringed its patents forced the lab to stop providing such services.

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[5] Myriad filed the first patent application leading to the patents in suit covering isolated BRCA1 DNA and associated diagnostic methods in August 1994. The first resulting patent, the '473 patent, issued on December 2, 1997. Myriad filed the first application leading to the patents in suit covering isolated BRCA2 DNA and associated diagnostic methods in December 1995, and the first such patent, the '492 patent, issued on November 17, 1998.

The first sign of a dispute came in early 1998. At that time, Dr. Kazazian recalls a dinner with Dr. Mark Skolnick, inventor and Chief Science Officer at Myriad. At the dinner, Skolnick informed Kazazian that Myriad was planning to stop GDL from providing clinical *BRCA* testing in light of Myriad's patents. A month or two later, in May 1998, Kazazian received a letter from William A. Hockett, Director of Corporate Communications at Myriad. The letter stated that Myriad knew that Kazazian was currently providing *BRCA1* diagnostic testing services, and that Myriad, as patent holder of five U.S. patents covering the isolated *BRCA1* gene and diagnostic testing, was making available to select institutions a collaborative license. Attached to the letter was a copy of Myriad's collaborative agreement, which proposed severely limiting GDL's testing services to certain tests for patients of Ashkenazi Jewish descent. Plaintiff Harry Ostrer, M.D, a researcher at New York University ("NYU") School of Medicine, received the same letter and collaborative agreement in May 1998, although his laboratory did not, at the time, provide such testing services. Rather, Ostrer sent patient samples to GDL for *BRCA* genetic testing.

Months later, in August 1998, Dr. Kazazian received a second letter, this time from George A. Riley of the law firm O'Melveny & Myers LLP. The letter identified by number five Myriad patents "covering, among other things, the BRCA1 gene sequence . . . and methods for detecting alterations in the BRCA1 sequence." J.A. 1145. The letter also indicated that it "has come to Myriad's attention that you are engaged in commercial testing activities that infringe Myriad's patents," and that "[u]nless and until a licensing arrangement is completed . . . you should cease all infringing testing activity." *Id.* The letter noted, however, that the cease-and-desist notification did not apply to research testing "for the purpose of furthering non-commercial research programs, the results of which are not provided to the patient and for which no money is received from the patient or the patient's insurance." *Id.*

In June 1999, Robert Terrell, the General Counsel for the University of Pennsylvania, received a similar cease-and-desist letter from Christopher Wight, Myriad's General Counsel. The letter stated, "It has come to our attention that Dr. Haig H. Kazazian, Jr. of the University of Pennsylvania is continuing to willfully engage in commercial BRCA1 and BRCA2 genetic testing activities, in violation of the University of Pennsylvania's previous assurances that such commercial testing activities would be discontinued." J.A. 2890. Terrell responded to Wight by letter on September 10, 1999, stating that "the University agrees that it will not accept samples for BRCA1 research testing from third parties." J.A. 2891. Kazazian thus informed Dr. Ostrer that GDL would no longer be accepting patient samples for *BRCA* testing from him or anyone else as a result of the patent infringement assertions made by Myriad. As a result, Ostrer started sending patient samples for *BRCA* genetic testing to Myriad, which became (and remains today) the only provider of such services in the United States.

During this period, Myriad also initiated several patent infringement suits against entities providing clinical *BRCA* testing. Myriad filed suit against Oncormed Inc. in 1997 and again in 1998, *Myriad Genetics v. Oncormed*, Nos. 2:97-cv-922, 2:98-cv-35 (D. Utah), and the University of Pennsylvania in 1998, *Myriad Genetics v. Univ. of Pa.*, No. 2:98-cv-829 (D. Utah). Both lawsuits were later dismissed without prejudice after each defendant agreed to discontinue all allegedly infringing activity.

None of the plaintiffs besides Drs. Kazazian, Ganguly, and Ostrer, allege that Myriad directed any letters or other communications regarding its patents at them. Rather, the other researchers and medical organization members state simply that knowledge of Myriad's vigorous enforcement of its patent rights against others stopped them from engaging in clinical *BRCA* genetic testing, although they have the personnel, expertise, and facilities as well as the desire to provide such testing. The patient plaintiffs state that they have been unable to obtain any *BRCA* genetic testing or their desired *BRCA* testing, either covered by their insurance or at a price that they can afford, because of Myriad's patent protection.

Like the other researchers, Dr. Kazazian states that if Myriad's patents were held invalid, he and Dr. Ganguly would be able to resume *BRCA* testing within a matter of a few weeks. He notes, however, that this is only if they "decided to resume BRCA testing." J.A. 2852. Ganguly concurs, stating that if the patents were invalidated, "I would immediately consider resuming BRCA testing in my laboratory."

J.A. 2892. Dr. Ostrer[6] also indicates that his lab has all the personnel, facilities, and expertise necessary to undertake clinical *BRCA* testing and emphatically states that his lab "would immediately begin to perform BRCA1/2-related genetic testing upon invalidation of the Myriad patents." J.A. 2936-38.

IV.

After Plaintiffs filed suit, Myriad moved to have the case dismissed, alleging that the Plaintiffs lacked standing to bring a declaratory judgment suit challenging the validity of its patents. The district court disagreed, however, holding that the Plaintiffs had established Article III standing under the "all the circumstances" test articulated by the Supreme Court in *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118, 127 (2007). *DJ Op.*, 669 F. Supp. 2d at 385-92. The court first found that Myriad had engaged in sufficient "affirmative acts" based on the company's assertion of its "right to preclude others from engaging in *BRCA1/2* genetic testing through personal communications, cease-and-desist letters, licensing offers, and litigation," the result of which was "the widespread understanding that one may engage in *BRCA1/2* testing at the risk of being sued for infringement liability by Myriad." *Id.* at 390. Myriad's actions, the court concluded, had placed "the Plaintiffs in precisely the situation that the Declaratory Judgment Act was designed to address: the Plaintiffs have the ability and desire to engage in *BRCA1/2* testing as well as the belief that such testing is within their rights, but cannot do so without risking infringement liability." *Id.*

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[6] On July 27, 2011, two days before we issued our initial, now-vacated decision in this case, Myriad notified the court that Dr. Ostrer was leaving NYU to assume a position at the Albert Einstein College of Medicine and Montefiore Medical Center, effective August 29, 2011. In response, Plaintiffs submitted a supplemental declaration from Dr. Ostrer stating that, in his new position, he still seeks to undertake BRCA diagnostic testing, still has the resources and expertise to conduct such testing, and would immediately do so if Myriad's patents were invalidated. Following remand from the Supreme Court, we have also received from Myriad a related "suggestion of mootness" and motion to remand or dismiss. We declined the suggestion and denied the motion. We now review this case on the facts and arguments briefed and presented to us.

In so holding, the court rejected Myriad's argument that there must be some act directed toward the Plaintiffs, noting that Myriad had, in fact, taken affirmative acts toward plaintiffs Dr. Kazazian and Dr. Ganguly. *Id.* at 387-88. The court also rejected Myriad's arguments that the cease-and-desist letter sent to plaintiff Kazazian was too old to support declaratory judgment jurisdiction and that the legal actions brought against third parties could not be considered in the jurisdictional analysis. *Id.* at 388-89. The court concluded that rigid adherence to either of these requirements would be inconsistent with *MedImmune*'s mandate that the court assess the facts alleged under all the circumstances. *Id.*

The district court also found that the Plaintiffs had alleged sufficient meaningful preparations for infringement to establish declaratory judgment jurisdiction. *Id.* at 390-92. With respect to the researchers, the court held it was sufficient that they were all "ready, willing, and able" to begin *BRCA1/2* testing within the normal course of their laboratories' research, rejecting Myriad's argument that they needed to allege specific preparatory activities. *Id.* at 390-91. The court also rejected Myriad's argument that plaintiffs Kazazian and Ganguly testified only that they would "consider" engaging in allegedly infringing activities, concluding that the proper focus of the inquiry is whether they are meaningfully prepared, not whether they have made a final, conclusive decision to engage in such activities. *Id.* at 391 n.18.

The parties then moved for summary judgment on the merits of Plaintiffs' § 101 challenge to Myriad's patent claims. The district court held for Plaintiffs, concluding that the fifteen challenged claims were drawn to non-patentable subject matter and thus invalid under § 101. *SJ Op.*, 702 F. Supp. 2d at 220-37. Regarding the composition claims, the court held that isolated DNA molecules fall within the judicially created "products of nature" exception to § 101 because such isolated DNAs are not "markedly different" from native DNAs. *Id.* at 222, 232 (quoting *Diamond v. Chakrabarty*, 447 U.S. 303 (1980)). The court relied on the fact that, unlike other biological molecules, DNAs are the "physical embodiment of information," and that this information is not only preserved in the claimed isolated DNA molecules, but also essential to their utility as molecular tools. *Id.* at 228-32.

Turning to the method claims, the court held them patent ineligible under this court's then-definitive machine-or-transformation test. *Id.* at 233 (citing *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008) (en banc), *aff'd on other grounds*, *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010)). The court held that the claims covered "analyzing" or "comparing" DNA sequences by any method, and thus covered mental processes independent of any physical transformations. *Id.* at 233-35. In so holding, the court distinguished Myriad's claims from those at issue in *Mayo* based on the "determining" step in the latter being construed to include the extraction and measurement of metabolite levels from a patient sample. *SJ Op.*, 702 F. Supp. 2d at 234-35 (citing *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 628 F.3d 1347, 1350 (Fed. Cir. 2010), *rev'd,* 132 S. Ct. 1289 (2012)). Alternatively, the court continued, even if the claims could be read to include the transformations associated with isolating and sequencing human DNA, these transformations would constitute no more than preparatory data-gathering steps. *Id.* at 236 (citing *In re Grams*, 888 F.2d 835, 840 (Fed. Cir. 1989)). Finally, the court held that the one method claim to "comparing" the growth rate of cells claimed a basic scientific principle and that the transformative steps amounted to only preparatory data gathering. *Id.* at 237.

Myriad appealed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

I. Declaratory Judgment Jurisdiction

A.

The first question we must address is whether the district court correctly exercised declaratory judgment jurisdiction over this suit. The Declaratory Judgment Act provides that, "In a case of actual controversy within its jurisdiction . . . any court of the United States . . . may declare the rights and other legal relations of any interested party seeking such declaration, whether or not further relief is or could be sought." 28 U.S.C. § 2201(a). The phrase "a case of actual controversy" in the Act refers to the types of "cases" and "controversies" that are justiciable under Article III of the U.S. Constitution. *Aetna Life Ins. v. Haworth*, 300 U.S. 227, 239-40 (1937).

Although no bright-line rule exists for determining whether a declaratory judgment action satisfies Article III's case-or-controversy requirement, the Supreme Court has held that the dispute must be "definite and concrete, touching the legal relations of parties having adverse legal interests," "real and substantial," and "admi[t] of specific relief through a decree of a conclusive character, as distinguished from an opinion advising what the law would be upon a hypothetical state of facts." *MedImmune*, 549 U.S. at 127 (quoting *Aetna Life*, 300 U.S. at 240-41). "Basically, the question in each case is whether the facts alleged, under all the circumstances, show that there is a substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment." *Id.* (quoting *Md. Cas. Co. v. Pac. Coal & Oil Co.*, 312 U.S. 270, 273 (1941)).

In applying *MedImmune*'s all-the-circumstances test to a declaratory judgment action, we are guided by the Supreme Court's three-part framework for determining whether an action presents a justiciable Article III controversy: standing, ripeness, and mootness. *See Caraco Pharm. Labs., Ltd. v. Forest Labs., Inc.*, 527 F.3d 1278, 1291 (Fed. Cir. 2008). In this case, the parties have framed the jurisdictional issue as one of standing. *See MedImmune*, 549 U.S. at 128 n.8. ("The justiciability problem that arises, when the party seeking declaratory relief is himself preventing the complained-of injury from occurring, can be described in terms of standing . . . or . . . ripeness." (internal citations omitted)).

"[T]he irreducible constitutional minimum of standing contains three elements." *Lujan v. Defenders of Wildlife*, 504 U.S. 555, 560 (1992). "First, the plaintiff must have suffered an injury in fact—an invasion of a legally protected interest which is (a) concrete and particularized, and (b) actual or imminent, not conjectural or hypothetical." *Id.* (internal citations and quotations omitted). "Second, there must be a causal connection between the injury and the conduct complained of–the injury has to be 'fairly . . . trace[able] to the challenged action of the defendant . . . .'" *Id.* (quoting *Simon v. E. Ky. Welfare Rights Org.*, 426 U.S. 26, 41-42 (1976)). "Third, it must be 'likely,' as opposed to merely 'speculative,' that the injury will be 'redressed by a favorable decision.'" *Id.* at 561 (quoting *Simon*, 426 U.S. at 38, 43).

"Whether an actual case or controversy exists so that a district court may entertain an action for a declaratory judgment of non-infringement and/or invalidity is governed by Federal Circuit law." *MedImmune, Inc. v. Centocor, Inc.*, 409 F.3d 1376, 1378 (Fed. Cir. 2005), *overruled on other grounds*, *MedImmune*, 549 U.S. at 130-31. Following *MedImmune*, this court has held that, to establish an injury in fact traceable to the patentee, a declaratory judgment plaintiff must allege both (1) an affirmative act by the patentee related to the enforcement of his patent rights, *SanDisk Corp. v. STMicroelecs., Inc.*, 480 F.3d 1372, 1380-81 (Fed. Cir. 2007), and (2) meaningful preparation to conduct potentially infringing activity, *Cat Tech LLC v. TubeMaster, Inc.*, 528 F.3d 871, 880 (Fed. Cir. 2008). We review the exercise of declaratory judgment jurisdiction in light of a particular set of facts *de novo*. *SanDisk Corp.*, 480 F.3d at 1377.

B.

Myriad challenges the district court's jurisdictional decision on the grounds that Myriad and the Plaintiffs do not have adverse legal interests and that Plaintiffs have failed to allege a controversy of sufficient immediacy and reality to warrant the issuance of a declaratory judgment. Specifically, Myriad argues that Plaintiffs have failed to allege any "affirmative acts" by Myriad within the past ten years relating to the patents in suit or directed at any Plaintiff. According to Myriad, the district court erred by relying on "stale communications" directed at Drs. Kazazian, Ganguly, and Ostrer over a decade ago, as well as ten-year-old licensing and litigation activities directed at third parties, and thus exercised jurisdiction based solely on Plaintiffs' subjective fear of suit, arising from rumor and innuendo in the research community.

Plaintiffs respond that they have standing under *MedImmune*'s all-the-circumstances test because, not only are they undisputedly prepared to immediately undertake potentially infringing activities, but also Myriad took sufficient affirmative acts with respect to the patents in suit. Regarding the latter, Plaintiffs assert that Myriad sued, threatened to sue, or demanded license agreements from every known institution offering *BRCA* clinical testing, including university labs directed by plaintiffs Kazazian, Ganguly, and Ostrer, forcing each to cease such testing. And, according to Plaintiffs, the awareness of Myriad's vigorous assertion of its patent rights still continues to suppress their ability to perform clinical *BRCA* testing, placing Plaintiffs in the very dilemma the Declaratory Judgment Act was intended to address: they must either proceed with *BRCA*-related activities and risk liability for patent infringement, or refrain from such activities despite believing Myriad's patents are invalid.

Under the facts alleged in this case, we conclude that one Plaintiff, Dr. Ostrer, has established standing to maintain this declaratory judgment suit. All Plaintiffs claim standing under the Declaratory Judgment Act based on the same alleged injury: that they cannot undertake the *BRCA*-related activities that they desire because of Myriad's enforcement of its patent rights covering *BRCA1/2*.[7] Only three plaintiffs, however, allege an injury traceable to Myriad; only Drs. Kazazian, Ganguly, and Ostrer allege affirmative patent enforcement actions directed at them by Myriad. Of these three, Dr. Ostrer clearly alleges a sufficiently real and imminent injury because he alleges an intention to actually and immediately engage in allegedly infringing *BRCA*-related activities. We address each in turn.

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[7] Certain patients also allege an injury based on their inability to gain access to affordable *BRCA* genetic testing because of Myriad's patent dominance of such services. While denial of health services can, in certain circumstances, state a judicially cognizable injury, *see Simon*, 426 U.S. at 40-41, Plaintiffs have not pressed this as an independent ground for standing. Moreover, we fail to see how the inability to afford a patented invention could establish an invasion of a legally protected interest for purposes of standing.

Although *MedImmune* relaxed this court's more restrictive "reasonable apprehension of suit" test for declaratory judgment jurisdiction, *SanDisk*, 480 F.3d at 1380, it did not alter "the bedrock rule that a case or controversy must be based on a *real* and *immediate* injury or threat of future injury that is *caused by the defendants*," *Prasco, LLC v. Medicis Pharm. Corp.*, 537 F.3d 1329, 1339 (Fed. Cir. 2008). Accordingly, following *MedImmune*, this court has continued to hold that declaratory judgment jurisdiction will not arise merely on the basis that a party learns of the existence of an adversely held patent, or even perceives that such a patent poses a risk of infringement, in the absence of some affirmative act by the patentee. *SanDisk*, 480 F.3d at 1380-81. Thus, without defining the outer boundaries of declaratory judgment jurisdiction, we have held that "where a patentee asserts rights under a patent based on certain identified ongoing or planned activity of another party, and where that party contends that it has the right to engage in the accused activity without license, an Article III case or controversy will arise . . . ." *Id.* at 1381; *see also Prasco*, 537 F.3d at 1338 ("A patentee can cause . . . an injury [sufficient to create an actual controversy] in a variety of ways, for example, by creating a reasonable apprehension of an infringement suit, [or] demanding the right to royalty payments." (internal citations omitted)).

In this case, Myriad demanded a royalty under its patents from Dr. Ostrer based on his clinical

BRCA-related activities. In May 1998, Myriad's Director of Corporate Communications sent Ostrer a letter proposing a collaborative license. The letter stated that Myriad was aware that Ostrer was either currently providing, or was interested in initiating, *BRCA1* diagnostic testing services and that Myriad, as holder of U.S. patents covering the *BRCA1* gene and diagnostic testing of *BRCA1*, was making available to his institution, NYU Medical Center, a limited collaborative license. The collaborative license required NYU to make a payment to Myriad for each non-research *BRCA* test performed.

At the same time, as Ostrer was aware, Myriad was asserting its patent rights against other similarly situated parties, a fact to be considered in assessing the existence of an actual controversy under the totality of circumstances. *See Micron Tech., Inc. v. Mosaid Techs., Inc.*, 518 F.3d 897, 901 (Fed. Cir. 2008). Soon after Ostrer received Myriad's letter, Dr. Kazazian informed him that, because of Myriad's assertion of its patent rights against him, GDL would no longer be accepting patient samples for *BRCA* genetic testing. Myriad's assertion of its patent rights against Kazazian escalated into a patent infringement suit by Myriad against the University of Pennsylvania, which was later dismissed without prejudice after the University agreed to cease all accused *BRCA* testing services. Myriad also sued Oncormed for patent infringement based on its *BRCA* genetic testing services. As a result of Myriad's patent enforcement actions, Dr. Ostrer was forced to send all patient samples to Myriad, now the sole provider of *BRCA* diagnostic testing services.

Dr. Ostrer, on the other hand, maintains that he could have proceeded with his *BRCA*-related clinical activities without taking a license from Myriad. This assertion is based on his belief that the patents Myriad claims cover such activities are invalid because genes are patent-ineligible products of nature. Acting on his belief, Ostrer seeks in this lawsuit a declaration of his right to undertake *BRCA*-related clinical activities without a license. Accordingly, Myriad and Dr. Ostrer have taken adverse legal positions regarding whether or not Ostrer can engage in *BRCA* genetic testing without infringing any valid claim to "isolated" *BRCA* DNAs or methods of "analyzing" or "comparing" *BRCA* sequences, as recited in Myriad's patents. *See Aetna Life*, 300 U.S. at 242 (holding declaratory judgment jurisdiction existed when "the parties had taken adverse positions with respect to their existing obligations" on an insurance contract).

Dr. Ostrer has also alleged a controversy of sufficient reality and immediacy, *MedImmune*, 549 U.S. at 127; he has alleged a concrete and actual injury traceable to Myriad's assertion of its patent rights, *see Lujan*, 504 U.S. at 560. First, Ostrer seeks to undertake specific *BRCA*-related activities—*BRCA* diagnostic testing—for which Myriad has demanded a license under specific patents—those that cover the isolated *BRCA* genes and *BRCA* diagnostic testing. Thus, Ostrer does not request "an opinion advising what the law would be upon a hypothetical state of facts," *Aetna Life*, 300 U.S. at 241, but rather whether his proposed *BRCA* testing services are covered by valid patent claims to "isolated" *BRCA* genes and methods of "comparing" the genes' sequences. Second, Ostrer not only has the resources and expertise to immediately undertake clinical *BRCA* testing, but also states unequivocally that he will immediately begin such testing. In contrast to Ostrer, who alleges an actual and imminent injury for purposes of standing, Drs. Kazazian and Ganguly allege only that they will "consider" resuming *BRCA* testing. These "'some day' intentions" are insufficient to support an "actual or imminent" injury for standing "without . . . any specification of *when* the some day will be." *Lujan*, 504 U.S. at 564. As a result, Drs. Kazazian and Ganguly do not have standing.

Myriad seeks to avoid this result based on the timing of its enforcement actions. Specifically, Myriad argues that time has extinguished the immediacy and reality of any controversy, relying on language that hearkens back to our pre-*MedImmune* reasonable apprehension of suit test. *See, e.g.*, Appellants' Br., 2010 WL 4600106, at 26 ("[A] patentee's ten-year silence presumptively extinguishes any reasonable objective fear of suit."). We disagree. In many cases a controversy made manifest by a patentee's affirmative assertion of its patent rights will dissipate as market players and products change. In this case, however, the relevant circumstances surrounding Myriad's assertion of its patent rights have not changed despite the passage of time.[8]

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[8] Myriad's analogy to laches is also unconvincing. Laches bars the recovery of pre-filing damages; it does not preclude a patent action for prospective relief, the type of relief sought here. *See A.C. Aukerman Co. v. R.L. Chaides Const. Co.*, 960 F.2d 1020, 1041 (Fed. Cir. 1992) (*en banc*) ("[L]aches bars relief on a patentee's claim only with respect to damages accrued prior to suit.").

Myriad's active enforcement of its patent rights forced Dr. Ostrer, as well as every other similarly situated researcher and institution, to cease performing the challenged *BRCA* testing services, leaving Myriad as the sole provider of *BRCA* clinical testing to patients in the United States. Since that time, neither the accused activities nor the parties' positions have changed. First, Myriad does not allege that genetic testing technology has changed in any way that renders its past assertions of its patent rights irrelevant to Ostrer's currently proposed *BRCA* testing. Rather, the patents cover, as Myriad asserted in the late 1990s, the basic components of any such test: the isolated *BRCA* genes and the diagnostic step of comparing the genes' sequences.

Second, ever since Myriad's enforcement efforts eliminated all competition, Myriad and Ostrer have not altered their respective positions. Ostrer, still laboring under Myriad's threat of infringement liability, has not attempted to provide *BRCA* testing; yet, as a researcher, he remains in the same position with respect to his ability and his desire to provide *BRCA* testing as in the late 1990s. Furthermore, nothing in the record suggests that any researcher or institution has successfully attempted to compete with Myriad, or that Myriad has in any way changed its position with regard to its patent rights. Just as active enforcement of one's patent rights against others can maintain a real and immediate controversy despite the passage of time, *see Micron*, 518 F.3d at 901, so too can the successful assertion of such rights when the relevant circumstances remain unchanged. Thus, consistent with the purpose of the Declaratory Judgment Act, Ostrer need not risk liability and treble damages for patent infringement before seeking a declaration of his contested legal rights. *See MedImmune*, 549 U.S. at 134.

Myriad also argues that the record refutes Ostrer's claim that he has been restrained from engaging in *BRCA*-related gene sequencing. Specifically, Myriad argues that since Myriad published its discoveries of the *BRCA1* and *BRCA2* genes in October 1994 and March 1996, respectively, over 18,000 scientists have conducted research on the *BRCA* genes and over 8,600 research papers have been published. Furthermore, according to Myriad, plaintiff Wendy Chung concedes that her lab currently conducts sequencing of *BRCA* genes. Yet, both Drs. Chung and Ostrer state that, although they conduct gene sequencing, they are forbidden from informing their research subjects of the results of their *BRCA* tests without first sending the samples to Myriad. Accordingly, Ostrer is restrained from the *BRCA*-related activity that he desires to undertake: clinical diagnostic testing.

Myriad's communications with Dr. Ostrer confirm this understanding. The licensing letter Myriad sent to Ostrer proposed a collaborative agreement giving NYU the right to perform "Research Tests" without payment to Myriad. J.A. 2967. "Research Tests" are defined as tests that further "non-commercial research programs, the results of which *are not provided to the patient* and for which no money is received." J.A 2965 (emphasis added). In contrast, the agreement requires payment to Myriad for each "Testing Service" performed, with "Testing Services" defined as "medical laboratory testing . . . for the presence or absence of BRCA1 mutations for the purpose of determining or predicting predisposition to, or assessing the risk of breast or ovarian cancer in humans." J.A. 2966-67. Thus, Myriad's patent enforcement actions never targeted the non-clinical *BRCA* research now cited by Myriad, and Ostrer's ability to perform such research does not address the injury asserted here.

Finally, Myriad argued in its reply brief and at oral argument that Plaintiffs' declaratory action will not afford them the relief they want, a requirement for standing. *Lujan*, 504 U.S. at 560-61; *see also MedImmune*, 549 U.S. at 127 n.7 ("[A] litigant may not use a declaratory-judgment action to obtain piecemeal adjudication of defenses that *would not finally and conclusively resolve* the underlying controversy."). Specifically, Myriad asserts that because Plaintiffs have challenged just fifteen composition and method claims, while admitting that other unchallenged claims to *BRCA* probes and primers will still prevent them from engaging in *BRCA* sequencing, a favorable decision will not redress the Plaintiffs' alleged injury. Again, we disagree.

The Supreme Court has required only that it is "likely," rather than "merely 'speculative,'" that the alleged injury will be "redressed by a favorable decision." *Lujan*, 504 U.S. at 561. The Court has not required certainty. For example, in *Village of Arlington Heights v. Metropolitan Housing Development Corp.*, the Court held that the plaintiffs had standing to challenge a suburb's exclusionary zoning ordinance, as the ordinance stood as "an absolute barrier" to the housing development Metropolitan Housing Development Corp. ("MHDC") had contracted to provide in the village. 429 U.S.

252, 261 (1977). The Court noted that injunctive relief, while removing the "barrier" of the ordinance, would not "guarantee" that the housing would be built since MHDC still had to secure financing, qualify for federal subsidies, and carry through with construction. *Id.* The Court nevertheless recognized that "all housing developments are subject to some extent to similar uncertainties," and concluded that it was sufficient that there was a "substantial probability" that the housing development would be built. *Id.* at 261, 264.

In this case, Myriad's challenged composition and method claims undisputedly provide "an absolute barrier" to Dr. Ostrer's ability to undertake *BRCA* diagnostic testing activities, and a declaration of those claims' invalidity would remove that barrier. *See id.* at 261. Moreover, while there may be other patent claims directed to *BRCA* probes and primers that prevent Ostrer from performing *BRCA* diagnostic testing free of infringement liability, Myriad has failed to direct us to any specific unchallenged claim that will have that effect. And Plaintiffs' counsel stated at the first oral argument in this case that his clients can sequence the *BRCA* genes without using *BRCA* probes and primers. Oral Arg. at 34:07-25, 34:53-35:29 *available at* http://www.cafc.uscourts.gov/oral-argument-recordings/2010-1406/all. Accordingly, we decline to construe the asserted claims and decline to hold on this record that Dr. Ostrer's proposed *BRCA*-related activities would infringe unchallenged claims to primers and probes. We thus conclude that it is likely, not merely speculative, that Dr. Ostrer's injury will be redressed by a favorable decision.

Although we affirm the district court's decision to exercise declaratory judgment jurisdiction over this case, we do so on narrower grounds. The district court failed to limit its jurisdictional holding to affirmative acts by the patentee directed at specific Plaintiffs, *see SanDisk*, 480 F.3d at 1380-81, erroneously holding all the Plaintiffs had standing based on "the widespread understanding that one may engage in *BRCA1/2* testing at the risk of being sued for infringement liability by Myriad," *DJ Op.*, 669 F. Supp. 2d at 390. We disagree, and thus we reverse the district court's holding that the various plaintiffs other than Dr. Ostrer have standing to maintain this declaratory judgment action. Simply disagreeing with the existence of a patent on isolated DNA sequences or even suffering an attenuated, non-proximate, effect from the existence of a patent does not meet the Supreme Court's requirement for an adverse legal controversy of sufficient immediacy and reality to warrant the issuance of a declaratory judgment. *See MedImmune*, 549 U.S. at 127. The various organizational plaintiffs in this suit in particular were not the target of any enforcement action or offered license agreements by Myriad and had made no preparation to undertake potentially infringing activities. They accordingly suffered no injury and thus lack standing to bring this action. *See Prasco*, 537 F.3d at 1338-42; *Cat Tech*, 528 F.3d at 880-81.

Having found one plaintiff with standing to maintain this declaratory judgment action, *see Horne v. Flores*, 129 S. Ct. 2579, 2592-93 (2009), we may turn now to the merits of Myriad's appeal of the district court's summary judgment decision, which held all fifteen challenged composition and method claims invalid under § 101.

II. Subject Matter Eligibility

Under the Patent Act, "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101. The Supreme Court has consistently construed § 101 broadly, explaining that "[i]n choosing such expansive terms . . . modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope." *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010) (quoting *Chakrabarty*, 447 U.S. at 308).

The Supreme Court, however, has also consistently held that § 101, although broad, is not unlimited. *Id.* The Court's precedents provide three judicially created exceptions to § 101's broad patent-eligibility principles: "'Laws of nature, natural phenomena, and abstract ideas' are not patentable." *Mayo*, 132 S. Ct. at 1293 (quoting *Diamond v. Diehr*, 450 U.S. 175, 185 (1981)). The Court has also referred to those exceptions as precluding the patenting of mental processes, *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972), and products of nature, *Chakrabarty*, 447 U.S. at 313 ("[T]he relevant distinction for purposes of § 101 is . . . between products of nature . . . and human-made inventions."). The Court has explained that, although not required by the statutory text, "[t]he concepts covered by these exceptions are 'part of the storehouse of knowledge of all men . . . free to all men and reserved exclusively to none.'" *Bilski*, 130 S. Ct. at 3225 (quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)).

Plaintiffs challenge under § 101 Myriad's composition claims directed to "isolated" DNA molecules, its method claims directed to "analyzing" or "comparing" DNA sequences, and its claim to a method for screening potential cancer therapeutics. We address each in turn. Before reviewing the applicability of the Supreme Court's *Mayo* holding to the claims of the Myriad patents, however, it is important to state what this appeal is not about. It is not about whether individuals suspected of having an increased risk of developing breast cancer are entitled to a second opinion. Nor is it about whether the University of Utah, the owner of the instant patents, or Myriad, the exclusive licensee, has acted improperly in its licensing or enforcement policies with respect to the patents. The question is also not whether is it desirable for one company to hold a patent or license covering a test that may save people's lives, or for other companies to be excluded from the market encompassed by such a patent—that is the basic right provided by a patent, *i.e.*, to exclude others from practicing the patented subject matter. It is also not whether the claims at issue are novel or nonobvious or too broad. Those questions are not before us. It is solely whether the claims to isolated BRCA DNA, to methods for comparing DNA sequences, and to a process for screening potential cancer therapeutics meet the threshold test for patent-eligible subject matter under 35 U.S.C. § 101 in light of various Supreme Court holdings, particularly including *Mayo*. The issue is patent eligibility, not patentability.

We would further note, in the context of discussing what this case is not about, that patents on life-saving material and processes, involving large amounts of risky investment, would seem to be precisely the types of subject matter that should be subject to the incentives of exclusive rights. But disapproving of patents on medical methods and novel biological molecules are policy questions best left to Congress, and other general questions relating to patentability and use of patents are issues not before us. As will be seen, on the limited questions before us, we conclude that the composition claims and the screening claim involving growing a transformed host cell meet the standards for patent eligibility, while the claimed methods for "analyzing" or "comparing" do not.

A. Composition Claims: Isolated DNA Molecules

i.

The principal claims of the patents before us on remand relate to isolated DNA molecules. *Mayo* does not control the question of patent-eligibility of such claims. They are claims to compositions of matter, expressly authorized as suitable patent-eligible subject matter in § 101. As to those claims, the issue of patent-eligibility remains, as it was on the first appeal to this court, whether they claim patent-ineligible products of nature. We hold that they do not. The isolated DNA molecules before us are not found in nature. They are obtained in the laboratory and are man-made, the product of human ingenuity. While they are prepared from products of nature, so is every other composition of matter. All new chemical or biological molecules, whether made by synthesis or decomposition, are made from natural materials. For example, virtually every medicine utilized by today's medical practitioners, and every manufactured plastic product, is either synthesized from natural materials (most often petroleum fractions) or derived from natural plant materials. But, as such, they are different from natural materials, even if they are ultimately derived from them. The same is true of isolated DNA molecules.

ii.

Myriad argues that its challenged composition claims to "isolated" DNAs cover patent-eligible compositions of matter within the meaning of § 101. According to Myriad, the district court came to a contrary conclusion by (1) misreading Supreme Court precedent as excluding from patent eligibility all "products of nature" unless "markedly different" from naturally occurring ones; and (2) incorrectly focusing not on the differences between isolated and native DNAs, but on one similarity: their informational content. Rather, Myriad argues, an isolated DNA molecule is patent eligible because it is, as claimed, "a nonnaturally occurring manufacture or composition of matter" with "a distinctive name, character, and use." Appellants' Br., 2010 WL 4600106, at 41-42 (quoting *Chakrabarty*, 447 U.S. at 309-10). Myriad contends that isolated DNA does not exist in nature and that isolated DNAs, unlike native DNAs, can be used as primers and probes for diagnosing cancer. Moreover, Myriad asserts that an ultimately-derived-from "products of nature" exception not only would be unworkable, as every composition of matter is, at some level, composed of natural materials, but also would be contrary to this court's precedents, the PTO's 2001 *Utility*

Examination Guidelines, and Congress's role in enacting the patent laws. Regarding *Mayo*, Myriad argues that the Supreme Court's decision did not address or alter the established patent-eligibility test for composition claims, such that the standards announced in *Chakrabarty* still govern this appeal. To the extent that the general principles discussed in *Mayo* bear on the DNA claims, Myriad maintains that isolated DNA represents a nonnatural, man-made invention distinct from the lack of human ingenuity underlying the method claims there at issue.

Plaintiffs respond that claims to isolated DNA molecules fail to satisfy § 101 because such claims cover natural phenomena and products of nature. According to Plaintiffs, Supreme Court precedent establishes that a product of nature is not patent eligible even if, as claimed, it has undergone some highly useful change from its natural form. Rather, Plaintiffs assert, to be patent eligible a composition of matter must also have a distinctive name, character, and use, making it "markedly different" from the natural product. In this case, Plaintiffs conclude that because isolated DNAs retain part of the same nucleotide sequence as native DNAs, they do not have any "markedly different" characteristics. Furthermore, according to Plaintiffs, the isolated DNA claims preempt products and laws of nature, excluding anyone from working with the *BRCA* genes and the genetic information they convey. Under *Mayo*, Plaintiffs assert that any structural differences relative to the chromosomal *BRCA* genes do not add "enough" to the underlying natural genetic sequences to render Myriad's isolated DNA molecules patentable under § 101.

The government as amicus curiae does not defend the longstanding position of the PTO, a government agency, that isolated DNA molecules are patent eligible, arguing instead for a middle ground. In contrast, the government asserts, isolated and unmodified genomic DNAs are *not* patent eligible, but rather patent-ineligible products of nature, since their nucleotide sequences exist because of evolution, not man. Specifically, the government argues that DNA molecules engineered by man, including cDNAs,[9] are patent-eligible compositions of matter because, with rare exceptions, they do not occur in nature, either in isolation or as contiguous sequences within a chromosome.

At the first oral argument, the government illustrated its position by way of a so-called "magic microscope" test (an invention in and of itself, although probably not patent-eligible). Oral Arg. at 46:50-47:50. According to the government's test then, if an imaginary microscope could focus in on the claimed DNA molecule as it exists in the human body, the claim covers ineligible subject matter. The government thus argued that because such a microscope could focus in on the claimed isolated *BRCA1* or *BRCA2* sequences as they exist in the human body, the claims covering those sequences are not patent eligible. In contrast, the government contended, because an imaginary microscope could not focus *in vivo* on a cDNA sequence, which is engineered by man to splice together non-contiguous coding sequences (*i.e.*, exons), claims covering cDNAs are patent eligible.

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[9] According to the government, several of the composition claims at issue in this suit, including claim 2 of the '282 patent, are limited to cDNA and thus patent eligible. We agree.

In sum, although the parties and the government appear to agree that isolated DNAs are compositions of matter, they disagree on whether and to what degree such molecules fall within the exception for products of nature. As set forth below, we conclude that the challenged claims to isolated DNAs, whether limited to cDNAs or not, are directed to patent-eligible subject matter under § 101.

iii.

While *Mayo* and earlier decisions concerning method claim patentability provide valuable insights and illuminate broad, foundational principles, the Supreme Court's decisions in *Chakrabarty* and *Funk Brothers* set out the primary framework for deciding the patent eligibility of compositions of matter, including isolated DNA molecules.[10]

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[10] Other Supreme Court decisions cited by the parties and amici relating to patented manufactures and compositions of matter were decided based on lack of novelty, not patent-eligible subject matter. In *American Wood-Paper Co. v. Fibre Disintegrating Co.*, the Court held the challenged patent "void for want of novelty in the manufacture patented," because the "[p]aper-pulp obtained from various vegetable substances was in common use before the original patent was granted . . . , and whatever may be said of their process for obtaining it, the product was in no sense new." 90 U.S. 566, 596 (1874). Similarly, in *Cochrane v. Badische Anilin & Soda Fabrik*, the Court held that a claim to artificial alizarine covered an old and well-known substance, the alizarine of madder, which could not be patented although made artificially for the first time. 111 U.S. 293, 311 (1884); *see also id.* at 308-09 ("It is very plain that the specification of the original patent, No. 95,465, states the invention to be a process for preparing alizarine, *not as a new substance prepared for the first time*, but as the substance

In *Chakrabarty*, the Court addressed the question whether a man-made, living microorganism is a patent-eligible manufacture or composition of matter within the meaning of § 101. 447 U.S. at 305, 307. The microorganisms were bacteria genetically engineered with four naturally occurring DNA plasmids, each of which enabled the breakdown of a different component of crude oil. *Id.* at 305, 305 n.1. The bacteria, as a result, could break down multiple components of crude oil, a trait possessed by no single naturally occurring bacterium and of significant use in more efficiently treating oil spills. *Id.* at 305, 305 n.2. The Court held that the bacteria qualified as patent-eligible subject matter because the "claim is not to a hitherto unknown natural phenomenon, but to a non-naturally occurring manufacture or composition of matter—a product of human ingenuity 'having a distinctive name, character [and] use.'" *Id.* at 309-10 (quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887)).

To underscore the point, the Court compared Chakrabarty's engineered bacteria with the mixed bacterial cultures found unpatentable in *Funk Brothers*, again casting this case, more relating to obviousness, in terms of § 101. *See Parker v. Flook*, 437 U.S. 584, 591 (1978); *Benson*, 409 U.S. at 67. In *Funk Brothers*, the patentee discovered that certain strains of nitrogen-fixing bacteria associated with leguminous plants do not mutually inhibit each other. 333 U.S. at 129-30. Based on that discovery,

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already known as alizarine, to be prepared, however, by the new process, which process is to be the subject of the patent, and is the process of preparing the *known product* alizarine from anthracine." (emphases added)).

the patentee produced (and claimed) mixed cultures of nitrogen-fixing species capable of inoculating a broader range of leguminous plants than single-species cultures. *Id.* The Court held that the bacteria's cooperative qualities were, "like the heat of the sun, electricity, or the qualities of metals," the "work of nature," and thus not patentable. *Id.* at 130. The Court also held that applying the newly discovered bacterial compatibility to create a mixed culture was not a patentable advance because no species acquired a different property or use. *Id.* at 131. The *Chakrabarty* Court thus concluded that what distinguished Chakrabarty's oil-degrading bacteria from the mixed cultures claimed in *Funk Brothers*, and made the former patent-eligible, was that Chakrabarty's bacteria had "markedly different characteristics from any [bacterium] found in nature" based on the efforts of the patentee. *Chakrabarty*, 447 U.S. at 310.

One distinction, therefore, between products of nature and human-made invention for purposes of § 101 turns on a change in the claimed composition's identity compared with what exists in nature. Specifically, the Supreme Court has drawn a line between compositions that, even if arrayed in useful combinations or harnessed to exploit newly discovered properties, have similar characteristics as in nature, and compositions that human intervention has given "markedly different," or "distinctive," characteristics. *Id.* (citing *Hartranft*, 121 U.S. at 615); *see also Am. Fruit Growers v. Brogdex Co.*, 283 U.S. 1, 11 (1931). Applying this test to the isolated DNAs in this case, the challenged claims are drawn to patent-eligible subject matter because the claims cover molecules that are markedly different—have a distinctive chemical structure and identity—from those found in nature.

It is undisputed that Myriad's claimed isolated DNAs exist in a distinctive chemical form—as distinctive chemical molecules—from DNAs in the human body, *i.e.*, native DNA. Natural DNA exists in the body as one of forty-six large, contiguous DNA molecules. Each of those DNA molecules is condensed and intertwined with various proteins, including histones, to form a complex tertiary structure known as chromatin that makes up a larger structural complex, a chromosome. *See supra*, Figure 3. Inside living cells, the chromosomes are further encapsulated within a series of membranes and suspended in a complex intracellular milieu.

Isolated DNA, in contrast, is a free-standing portion of a larger, natural DNA molecule. Isolated DNA has been cleaved (*i.e.*, had covalent bonds in its backbone chemically severed) or synthesized to consist of just a fraction of a naturally occurring DNA molecule. For example, the *BRCA1* gene in its native state resides on chromosome 17, a DNA molecule of around eighty million nucleotides. Similarly, *BRCA2* in its native state is located on chromosome 13, a DNA of approximately 114 million nucleotides. In contrast, isolated *BRCA1* and *BRCA2*, with introns, each consists of just 80,000 or so nucleotides. And without introns, *BRCA2* shrinks to approximately 10,200 nucleotides and *BRCA1* to just around 5,500 nucleotides. Furthermore, claims 5 and 6 of the '282 patent cover isolated DNAs, *e.g.*, primers or probes, having as few as fifteen nucleotides of a *BRCA* sequence. Accordingly, *BRCA1* and *BRCA2* in their isolated states are different molecules from DNA that exists in the body; isolated DNA results from human intervention to cleave or synthesize a discrete portion of a native chromosomal DNA, imparting on that isolated DNA a distinctive chemical identity as compared to native DNA.

As the above description indicates, isolated DNA is not just purified DNA. Purification makes pure what was the same material, but was combined, or contaminated, with other materials. Although isolated DNA is removed from its native cellular and chromosomal environment, it has also been manipulated chemically so as to produce a molecule that is markedly different from that which exists in the body. Accordingly, this is not a situation, as in *Parke-Davis & Co. v. H.K. Mulford Co.*, in which purification of adrenaline resulted in the *identical* molecule, albeit being "for every practical purpose a new thing commercially and therapeutically." 189 F. 95, 103 (C.C.S.D.N.Y. 1911). Judge Learned Hand's opinion for the district court in that oft-cited case held the purified "Adrenalin" to be patent-eligible subject matter. *Id.* The *In re Marden* cases are similarly inapposite, directed as they are to the patent ineligibility of purified natural elements—ductile uranium, 47 F.2d 957 (CCPA 1931), and vanadium, 47 F.2d 958 (CCPA 1931)—that are inherently ductile in purified form. While purified natural products thus may or may not qualify for patent under § 101, the isolated DNAs of the present patents constitute an *a fortiori* situation, where they are not only purified; they are different from the natural products in "name, character, and use." *Chakrabarty*, 447 U.S. at 309-10.[11]

Parke-Davis and *Marden* address a situation in which claimed compound A is purified from a physical mixture that contains compound A. In this case, the claimed isolated DNA molecules do not exist in nature within a physical mixture to be purified. They have to be chemically cleaved from their native chemical combination with other genetic materials. In other words, in nature, the claimed isolated DNAs are covalently bonded to such other materials. Thus, when cleaved, an isolated DNA molecule is not a purified form of a natural material, but a distinct chemical entity that is obtained by human intervention. *See Chakrabarty*, 447 U.S. at 313 ("the relevant distinction [is] between products of nature . . . and human-made inventions"). In fact, some forms of isolated DNA may require no purification at all, because DNAs can be chemically synthesized directly as isolated molecules.

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[11] *In re Bergy*, relating to a purified microorganism, 596 F.2d 952, 967-68 (CCPA 1979), was once a companion case to *Chakrabarty* but was vacated by the Supreme Court and remanded for dismissal as moot when the inventors withdrew their claim from the pending application. *Diamond v. Chakrabarty*, 444 U.S. 1028 (1980). Other CCPA cases cited by the parties and amici were not decided based on patent eligibility. In *In re Bergstrom*, the court held that pure prostaglandin compounds, PGE(2) and PGE(3), were improperly rejected as lacking novelty. 427 F.2d 1394, 1394 (CCPA 1970); *see Bergy*, 596 F.2d at 961 (recognizing *Bergstrom* as a case decided under § 102). Similarly in *In re Kratz*, the court held nonobvious claims to synthetically produced, substantially pure 2-methyl-2-pentenoic acid, a chemical that gives strawberries their flavor. 592 F.2d 1169, 1170 (CCPA 1979); *see also In re King*, 107 F.2d 618, 619 (CCPA 1939) (holding claims to vitamin C invalid for lack of novelty, as "[a]ppellants were not the first to discover or produce [vitamin C] in its pure form"); *In re Merz*, 97 F.2d 599, 601 (CCPA 1938) (holding claims to artificial ultramarine that contains non-floatable impurities invalid as not "inventive," and thus obvious).

The above analysis holding the isolated DNA molecules to be patent-eligible subject matter applies to all of the asserted composition claims on appeal in this case. However, as the government has pointed out, claim 2 of the '282 patent is narrower than claim 1 and reads only on cDNAs, which lack the non-coding introns present in the genomic *BRCA1* gene.[12] While, as we have held, all of the claimed isolated DNAs are eligible for patent as compositions of matter distinct from natural DNA, the claimed cDNAs are especially distinctive, lacking the non-coding introns present in naturally occurring chromosomal DNA. They are even more the result of human intervention into nature and are hence patent-eligible subject matter. The government, as noted earlier, has agreed with that conclusion. Br. United States, 2010 WL 4853320, at 14-17.

The dissent disparages the significance of a "chemical bond," presumably meaning a covalent bond, in distinguishing structurally between one molecular species and another. But a covalent bond is the defining boundary between one molecule and another, and the dissent's citation of Linus Pauling's comment that covalent bonds "make it convenient for the chemist to consider [the aggregate] as an independent molecular species" underlines the point.

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[12] Claims 2 and 7 of the '282 patent and claim 7 of the '492 patent recite isolated cDNA molecules.

The covalent bonds in this case connect different chemical moieties to one another.

Plaintiffs argue that because the claimed isolated DNAs retain the same nucleotide sequence as native DNAs, they do not have any "markedly different" characteristics. This approach, however, looks not at whether isolated DNAs are markedly different—have a distinctive characteristic—from naturally occurring DNAs, as the Supreme Court has directed, but at one similarity, albeit a key one: the information content contained in isolated and native DNAs' nucleotide sequences. Adopting this approach, the district court disparaged the patent eligibility of isolated DNA molecules because their genetic function is to transmit information. We disagree, as it is the distinctive nature of DNA molecules as isolated compositions of matter that determines their patent eligibility rather than their physiological use or benefit. Uses of chemical substances may be relevant to the nonobviousness of these substances or to method claims embodying those uses, but the patent eligibility of an isolated DNA is not negated because it has similar informational properties to a different, more complex natural material. The claimed isolated DNA molecules are distinct from their natural existence as portions of larger entities, and their informational content is irrelevant to that fact. We recognize that biologists may think of molecules in terms of their uses, but genes are in fact materials having a chemical nature and, as such, are best described in patents by their structures rather than by their functions. In fact, many different materials may have the same function (*e.g.*, aspirin, ibuprofen, and naproxen).

The district court in effect created a categorical rule excluding isolated genes from patent eligibility. *See SJ Op.*, 702 F. Supp. 2d at 228-29. But the Supreme Court has "more than once cautioned that courts 'should not read into the patent laws limitations and conditions which the legislature has not expressed.'" *Bilski*, 130 S. Ct. at 3226 (quoting *Diehr*, 450 U.S. at 182), and has repeatedly rejected new categorical exclusions from § 101's scope, *see id.* at 3227-28 (rejecting the argument that business method patents should be categorically excluded from § 101); *Chakrabarty*, 447 U.S. at 314-17 (same for living organisms). Contrary to the conclusions of the district court and the suggestions of Plaintiffs and some amici, § 101 applies equally to all putative inventions, and isolated DNA is not and should not be considered a special case for purposes of patent eligibility under existing law. *See, e.g.*, *SJ Op.*, 702 F. Supp. 2d at 185 ("DNA represents the physical embodiment of biological information, distinct in its essential characteristics from any other chemical found in nature."); Appellees' Suppl. Br. at 4-5 ("Unlike other chemicals, the information encoded by DNA reflects its primary biological function . . . .").

Under the statutory rubric of § 101, isolated DNA is a tangible, man-made composition of matter defined and distinguished by its objectively discernible chemical structure. Whether its unusual status as a chemical entity that conveys genetic information warrants singular treatment under the patent laws as the district court did is a policy question that we are not entitled to address. *Cf. Nat'l Fed'n of Indep. Bus. v. Sebelius*, 132 S. Ct. 2566, slip op. at 6 (2012) ("[W]e possess neither the expertise nor the prerogative to make policy judgments. Those decisions are entrusted to our Nation's elected leaders, who can be thrown out of office if the people disagree with them."). Congress is presumed to have been aware of the issue, having enacted a comprehensive patent reform act during the pendency of this case, and it is ultimately for Congress if it wishes to overturn case law and the long practice of the PTO to determine that isolated DNA must be treated differently from other compositions of matter to account for its perceived special function. We therefore reject the district court's unwarranted categorical exclusion of isolated DNA molecules.

Because isolated DNAs, not just cDNAs, have a markedly different chemical structure compared to native DNAs, we reject the government's earlier proposed "magic microscope" test, as it misunderstands the difference between science and invention and fails to take into account the existence of molecules as separate chemical entities. The ability to visualize a DNA molecule through a microscope, or by any other means, when it is bonded to other genetic material, is worlds apart from possessing an isolated DNA molecule that is in hand and usable. It is the difference between knowledge of nature and reducing a portion of nature to concrete form, the latter activity being what the patent laws seek to encourage and protect. The government's microscope could focus in on a claimed portion of any complex molecule, rendering that claimed portion patent ineligible, even though that portion never exists as a separate molecule in the body or anywhere else in nature, and may have an entirely different utility. That would discourage innovation. One cannot visualize a portion of a complex molecule, including a DNA containing a particular gene, and will it into isolation as a unique entity. Visualization does not cleave and isolate the particular DNA; that is the act of human invention.

The Supreme Court in *Mayo* focused on its concern that permitting patents on particular subject matter would prevent use by others of, in *Mayo*, the correlation recited in the method claims. Plaintiffs argue here that they are preempted from using the patented DNA molecules. The answer to that concern is that permitting patents on isolated genes does not preempt a law of nature. A composition of matter is not a law of nature. Moreover, as indicated earlier, a limited preemption is inherent in every patent: the right to exclude for a limited period of time. 35 U.S.C. § 154(a)(1) ("Every patent shall contain . . . a grant to the patentee, his heirs or assigns, of the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States . . . ."). When the patent expires, the public is entitled to practice the invention of the patent. That is true of all inventions; during the term of the patent, unauthorized parties are "preempted" from practicing the patent, but only for its limited term. The seven patents being challenged here all expire by December 18, 2015.[13] Any preemption thus is limited, very limited in the case of the present patents. Moreover, patents are rarely enforced against scientific research, even during their terms.

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[13] Specifically, the '441 patent will expire on August 12, 2014; the '473 patent will expire on December 2, 2014; the '999 and '001 patents will expire on January 20, 2015; the '282 patent will expire on May 5, 2015; and the '492 and '857 patents will expire on December 18, 2015.

The remand of this case for reconsideration in light of *Mayo* might suggest, as Plaintiffs and certain amici state, that the composition claims are mere reflections of a law of nature. Respectfully, they are not, any more than any product of man reflects and is consistent with a law of nature. Everything and everyone comes from nature, following its laws. But the compositions here are not natural products. They are the products of man, albeit following, as all materials do, laws of nature.

The dissent indicates that "elemental lithium (like other elements) would not be patentable subject matter, even if it could only be extracted from nature through an isolation process." But the isolation here is not a simple separation from extraneous materials, but conversion to a different molecular entity. And again, these facts are not before us, so we do not attempt to evaluate the patentability of one form of lithium over another. Courts decide cases; they do not draft comprehensive legal treatises. Suffice it to say, however, that if lithium is found in the earth as other than elemental lithium because it reacts with air and water to form, for example, lithium oxide or lithium hydroxide, it is a different material. A lithium compound is not elemental lithium.

It is also important to dispute the dissent's analogy to snapping a leaf from a tree. With respect, no one could contemplate that snapping a leaf from a tree would be worthy of a patent, whereas isolating genes to provide useful diagnostic tools and medicines is surely what the patent laws are intended to encourage and protect. Snapping a leaf from a tree is a physical separation, easily done by anyone. Creating a new chemical entity is the work of human transformation, requiring skill, knowledge, and effort. *See Mayo*, 132 S. Ct. at 1294 ("While a scientific truth . . . is not a patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be.") (quoting *Mackay Radio & Tel. Co. v. Radio Corp. of Am.*, 306 U.S. 86, 94 (1939)).

The dissent also mentions several times in its opinion the "breathtaking[]" breadth of certain claims as grounds for objecting to their patentability. However, we do not have here any rejection or invalidation on the various grounds relating to breadth, such as in 35 U.S.C. § 112. The issue before us is patent eligibility under § 101, not the adequacy of the patents' disclosure to support particular claims. Nor is it lack of patentability for obviousness, as the dissent intimates, that is before us.

The dissent finally attempts to analogize the creation of the isolated DNAs in this case to the removal of a kidney from the human body, indicating that the latter does not create patent-eligible subject matter, hence the claimed isolated DNAs also do not. Such an analogy is misplaced. Extracting a kidney from a body does not result in a patent-eligible composition, as an isolated gene has been and should be. A kidney is an organ, not a well defined composition of matter or an article of manufacture specified by § 101. No one could confuse extensive research needed to locate, identify, and isolate a gene with the extraction of an organ from a body. One is what patents are intended to stimulate research on and hence are properly patent eligible, and the other, while obviously essential to human wellbeing, is not what patents are understood to cover under the patent statute. An isolated DNA is properly characterized as a composition of matter under § 101; no one would so characterize an isolated body organ.

Finally, our decision that isolated DNA molecules are patent eligible comports with the longstanding practice of the PTO and the courts. The Supreme Court has repeatedly stated that changes to longstanding practice should come from Congress, not the courts. In *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred International, Inc.*, the Court rejected the argument that plants did not fall within the scope of § 101, relying in part on the fact that "the PTO has assigned utility patents for plants for at least 16 years and there has been no indication from either Congress or agencies with expertise that such coverage is inconsistent with [federal law]." 534 U.S. 124, 144-45 (2001); *see also Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002) ("[C]ourts must be cautious before adopting changes that disrupt the settled expectations of the inventing community." (citing *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 28 (1997))); *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1347 (Fed. Cir. 2010) (en banc) (upholding a written description requirement separate from enablement based in part on *stare decisis*).

In this case, the PTO has issued patents relating to DNA molecules for almost thirty years. In the early 1980s, the Office granted the first human gene patents. *See* Eric J. Rogers, *Can You Patent Genes? Yes and No*, 93 J. Pat. & Trademark Off. Soc'y 19 (2010). It is estimated that the PTO has issued 2,645 patents claiming "isolated DNA" over the past twenty-nine years, J.A. 3710, and that by 2005, had granted 40,000 DNA-related patents relating to, in non-native form, genes in the human genome, Rogers, *supra* at 40. In 2001, the PTO issued *Utility Examination Guidelines*, which reaffirmed the agency's position that isolated DNA molecules are patent eligible, 66 Fed. Reg. 1092-94 (Jan. 5, 2001), and Congress has not indicated that the PTO's position is inconsistent with § 101. If the law is to be changed, and DNA inventions excluded from the broad scope of § 101, contrary to the settled expectation of the inventing and investing communities, the decision must come, not from the courts, but from Congress. The dissent mentions possible "adverse effects" that may occur if isolated DNAs are held to be patent eligible. But, respectfully, it is the adverse effects on innovation that a holding of ineligibility might cause. Patents encourage innovation and even encourage inventing around; we must be careful not to rope off far-reaching areas of patent eligibility.

Accordingly, we once again conclude that claims 1, 2, 5, 6, and 7 of the '282 patent; claims 1, 6, and 7 of the '492 patent; and claim 1 of the '473 patent directed to isolated DNA molecules recite patent-eligible subject matter under § 101. *Mayo* does not change that result. In so doing, we reiterate that the issue before us is *patent eligibility*, not *patentability*, about which we express no opinion.

II. Method Claims

We turn next to Myriad's challenged method claims. This court in its now-vacated decision of July

29, 2011, had held method claims 1 of the '999, '001, and '441 patents, as well as method claims 1 and 2 of the '857 patent—all of which consist of analyzing and comparing certain DNA sequences—not to be patent-eligible subject matter on the ground that they claim only abstract mental processes. In light of the Supreme Court's decision in *Mayo*, we reaffirm that prior holding. The Court made clear that such diagnostic methods in that case essentially claim natural laws that are not eligible for patent. Without expressly analyzing the instant method claims in the context of the Court's reasoning, but in light of the Court's holding, and in view of our own prior reasoning, set forth herein below, those method claims cannot stand.

In our prior decision, however, we reversed the district court's holding that claim 20 of the '282 patent was not eligible for patent. We did so on the ground, *inter alia*, that, in addition to the step of comparing the cells' growth rates, the claim also recites the steps of growing transformed cells and determining those growth rates. We relied on the fact that those steps were transformative. Although the Court has now held that certain transformative steps are not necessarily sufficient under § 101 if the recited steps only rely on natural laws, we once again, even in light of *Mayo*, arrive at the same conclusion of patent-eligibility because at the heart of claim 20 is a transformed cell, which is made by man, in contrast to a natural material.

A. Methods of "Comparing" or "Analyzing" Sequences

Myriad argued that its claims to methods of "comparing" or "analyzing" *BRCA* sequences satisfy the machine-or-transformation test because each requires a transformation—extracting and sequencing DNA molecules from a human sample—before the sequences can be compared or analyzed. According to Myriad, the district court failed to recognize the transformative nature of the claims by (1) misconstruing the claim term "sequence" as merely information, rather than a physical molecule; and (2) erroneously concluding, in the alternative, that Myriad's proposed transformations were mere data-gathering steps, rather than central to the purpose of the claims.

Plaintiffs responded that these method claims are drawn to the abstract idea of comparing one sequence to a reference sequence and preempt a phenomenon of nature—the correlation of genetic mutations with a predisposition to cancer. And, according to the Plaintiffs, limiting the claims' application to a specific technological field, *i.e.*, *BRCA* gene sequences, is insufficient to render the claims patent eligible. Plaintiffs also assert that the claims do not meet the machine-or-transformation test because the claims' plain language includes just the one step of "comparing" or "analyzing" two gene sequences.

We renew our conclusion that Myriad's claims to "comparing" or "analyzing" two gene sequences fall outside the scope of § 101 because they claim only abstract mental processes. *See Benson*, 409 U.S. at 67 ("Phenomena of nature, . . . mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work."). The claims recite, for example, a "method for screening a tumor sample," by "comparing" a first

BRCA1 sequence from a tumor sample and a second *BRCA1* sequence from a non-tumor sample, wherein a difference in sequence indicates an alteration in the tumor sample. '001 patent claim 1. This claim thus recites nothing more than the abstract mental steps necessary to compare two different nucleotide sequences: one looks at the first position in a first sequence; determines the nucleotide sequence at that first position; looks at the first position in a second sequence; determines the nucleotide sequence at that first position; determines if the nucleotide at the first position in the first sequence and the first position in the second sequence are the same or different, wherein the latter indicates an alteration; and repeats the process for the next position.

Limiting the comparison to just the *BRCA* genes or, as in the case of claim 1 of the '999 patent, to just the identification of particular alterations, fails to render the claimed process patent-eligible. As the Supreme Court has held, "the prohibition against patenting abstract ideas 'cannot be circumvented by attempting to limit the use of the formula to a particular technological environment.'" *Bilski*, 130 S. Ct. at 3230 (quoting *Diehr*, 450 U.S. at 191-92); *see also id.* at 3231 ("*Flook* established that limiting an abstract idea to one field of use . . . did not make the concept patentable."). Although the *application* of a formula or abstract idea in a process may describe patent-eligible subject matter, *id.* at 3230, Myriad's claims do not apply the step of comparing two nucleotide sequences in a process. Rather, the step of comparing two DNA sequences is the entire process that is claimed.

To avoid this result, Myriad attempts to read into its method claims additional, allegedly transformative steps. As described above, Myriad reads into its claims the steps of (1) extracting DNA from a human sample, and (2) sequencing the *BRCA* DNA molecule, arguing that both steps necessarily precede the step of comparing nucleotide sequences. The claims themselves, however, do not include either of these steps. The claims do not specify any action prior to the step of "comparing" or "analyzing" two sequences; the claims recite just the one step of "comparing" or "analyzing." Moreover, those terms' plain meaning does not include Myriad's proposed sample-processing steps; neither comparing nor analyzing means or implies "extracting" or "sequencing" DNA or otherwise "processing" a human sample.

Myriad claims that "comparing" and "analyzing" take on such meaning when read in light of the patent specifications. Specifically, Myriad argues that the specifications show that the claim term "sequence" refers not to information, but rather to a physical DNA molecule, whose sequence must be determined before it can be compared. That may be true, but the claims only recite mental steps, not the structure of physical DNA molecules.

Accordingly, Myriad's challenged method claims are indistinguishable from the claims the Supreme Court found invalid under § 101 in *Mayo*. In *Mayo*, the patents claimed methods for optimizing the dosage of thiopurine drugs administered to patients with gastrointestinal disorders. 132 S. Ct. at 1295. As written, the claimed methods included the steps of (a) "administering" a thiopurine drug to a subject, and/or (b) "determining" the drug's metabolite levels in the subject, wherein the measured metabolite levels are compared with predetermined levels to optimize drug dosage. *Id.* In holding that the claims satisfied § 101, this court concluded that, in addition to the "administering" step being transformative, the "determining" step was both transformative and central to the purpose of the claims. *Prometheus*, 628 F.3d at 1357. However, the Supreme Court held that the steps of administering and determining, combined with a correlative "wherein" clause, were not sufficiently transformative of what was otherwise a claim to a natural law. That holding governs Myriad's claims to methods of "comparing" and "analyzing" DNA sequences.

Myriad's other claims do not even include a *Mayo*-like step of "determining" the sequence of *BRCA* genes by, *e.g.*, isolating the genes from a blood sample and sequencing them, or any other putatively transformative step. Rather, the comparison between the two sequences can be accomplished by mere inspection alone. Accordingly, Myriad's claimed methods of comparing or analyzing nucleotide sequences are only directed to the abstract mental process of comparing two nucleotide sequences. As such, we hold claims 1 of the '999 patent, '001 patent, and '441 patent and claims 1 and 2 of the '857 patent invalid under § 101 for claiming patent-ineligible processes.

B. Method of Screening Potential Cancer Therapeutics

Lastly, we turn to claim 20 of the '282 patent, directed to a method for screening potential cancer therapeutics via changes in cell growth rates of transformed cells. The parties agree that those transformed cells arose from human effort; *i.e.*, they are not natural products. Plaintiffs nonetheless challenge claim 20 as directed to the abstract idea of comparing the growth rates of two cell populations and as preempting a basic scientific principle—that a slower growth rate in the presence of a potential therapeutic compound suggests that the compound is a cancer therapeutic. Plaintiffs therefore contend that claim 20 is indistinguishable from the claims held ineligible in *Mayo*. We disagree.

Claim 20 recites a method that comprises the steps of (1) growing host cells *transformed* with an altered *BRCA1* gene in the presence or absence of a potential cancer therapeutic, (2) determining the growth rate of the host cells with or without the potential therapeutic, and (3) comparing the growth rate of the host cells. Claim 20 thus recites a screening method premised on the use of "transformed" host cells. Those cells, like the patent-eligible cells in *Chakrabarty*, are not naturally occurring. Rather, they are derived by altering a cell to include a foreign gene, resulting in a man-made, transformed cell with enhanced function and utility. *See* '282 patent col.27 ll.28-33. The claim thus includes more than the abstract mental step of looking at two numbers and "comparing" two host cells' growth rates.

In *Mayo*, the Supreme Court invalidated claims directed to the relationship between concentrations of certain metabolites in the blood and the likelihood that a particular dosage of a thiopurine drug will be optimum, stating that steps of "administering" and "determining," coupled with a correlative "wherein" clause, were insufficient to differentiate the claimed method from the natural laws encompassed by the claims. In short, "to transform an unpatentable law of nature into a patent-eligible *application* of such a law, one must do more than simply state the law of nature while adding the words 'apply it'." 132 S. Ct. at 1294.

Here, claim 20 does do more; it does not simply apply a law of nature. Of course, all activity, whether chemical, biological, or physical, relies on natural laws. But, more to the point here is that claim 20 applies certain steps to transformed cells that, as has been pointed out above, are a product of man, not of nature. The Court, in its evaluation of the *Mayo* method claims, found that the additional steps of those claims were not sufficient to "transform" the nature of the claims from mere expression of natural laws to patent-eligible subject matter. By definition, however, performing operations, even known types of steps, on, or to create, novel, *i.e.*, transformed subject matter is the stuff of which most process or method invention consists. All chemical processes, for example, consist of hydrolyzing, hydrogenating, reacting, etc. In situations where the objects or results of such steps are novel and nonobvious, they should be patent-eligible. It is rare that a new reaction or method is invented; much process activity is to make new compounds or products using established processes. Thus, once one has determined that a claimed composition of matter is patent-eligible subject matter, applying various known types of procedures to it is not merely applying conventional steps to a law of nature. The transformed, man-made nature of the underlying subject matter in claim 20 makes the claim patent-eligible. The fact that the claim also includes the steps of determining the cells' growth rates and comparing growth rates does not change the fact that the claim is based on a man-made, non-naturally occurring transformed cell—patent-eligible subject matter.

Furthermore, the claim does not cover all cells, all compounds, or all methods of determining the therapeutic effect of a compound. Rather, it is tied to specific host cells *transformed* with specific genes and grown in the presence or absence of a specific type of therapeutic. Accordingly, we hold that claim 20 of the '282 patent recites patent-eligible subject matter under § 101. Whether such processes, including claim 20, meet other tests for patentability, such as novelty or nonobviousness, is not before us.

CONCLUSION

For the foregoing reasons, we affirm the district court's decision to exercise declaratory judgment jurisdiction over this case, we reverse the district court's grant of summary judgment with regard to Myriad's composition claims to isolated DNAs, including cDNAs, we affirm the district court's grant of summary judgment with regard to Myriad's method claims directed to comparing or analyzing gene sequences, and we reverse the district court's grant of summary judgment with regard to Myriad's method claim to screening potential cancer therapeutics via changes in cell growth rates of novel, man-made transformed cells.

AFFIRMED IN PART and REVERSED IN PART

COSTS

Costs to Myriad.

United States Court of Appeals for the Federal Circuit

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, THE AMERICAN COLLEGE OF MEDICAL GENETICS, THE AMERICAN SOCIETY FOR CLINICAL PATHOLOGY, THE COLLEGE OF AMERICAN PATHOLOGISTS, HAIG KAZAZIAN, MD, ARUPA GANGULY, PHD, WENDY CHUNG, MD, PHD, HARRY OSTRER, MD, DAVID LEDBETTER, PHD, STEPHEN WARREN, PHD, ELLEN MATLOFF, M.S., ELSA REICH, M.S., BREAST CANCER ACTION, BOSTON WOMEN'S HEALTH BOOK COLLECTIVE, LISBETH CERIANI, RUNI LIMARY, GENAE GIRARD, PATRICE FORTUNE, VICKY THOMASON, AND KATHLEEN RAKER,

Plaintiffs-Appellees,

v.

UNITED STATES PATENT AND TRADEMARK OFFICE,

Defendant,

and

MYRIAD GENETICS, INC.,

Defendant-Appellant,

and

LORRIS BETZ, ROGER BOYER, JACK BRITTAIN, ARNOLD B. COMBE, RAYMOND GESTELAND, JAMES U. JENSEN, JOHN KENDALL MORRIS, THOMAS PARKS, DAVID W. PERSHING, AND

MICHAEL K. YOUNG, IN THEIR OFFICIAL
CAPACITY AS DIRECTORS OF THE UNIVERSITY
OF UTAH RESEARCH FOUNDATION,

Defendants-Appellants.

2010-1406

Appeal from the United States District Court for the Southern District of New York in case No. 09-CV-4515, Senior Judge Robert W. Sweet.

MOORE, *Circuit Judge*, concurring in part.

I join the majority opinion with respect to standing and the patentability of the method claims at issue. I join the majority with respect to claims to isolated cDNA sequences, and concur in the judgment with respect to isolated DNA sequences. I write separately to explain my reasoning.

I.

The Patent Act, 35 U.S.C. § 101, allows "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof" to obtain a patent. The plain language of this statute only requires that an invention be "new and useful," and fall into one of four categories: a "process, machine, manufacture, or composition of matter." "Congress intended statutory subject matter to 'include anything under the sun that is made by man.'" *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) (quoting the statutory history).

While the plain language used by Congress did not limit the scope of patentable subject matter in the statute, the "Court's precedents provide three specific exceptions to § 101's broad patent-eligibility principles: 'laws of nature, physical phenomena, and abstract ideas.'" *Bilski v. Kappos*, 130 S. Ct. 3218, 3226 (2010) (quoting *Chakrabarty*, 447 U.S. at 309). These exceptions "rest[], not on the notion that natural phenomena are not processes [or other articulated statutory categories], but rather on the more fundamental understanding that they are not the kind of 'discoveries' that the statute was enacted to protect." *Parker v. Flook*, 437 U.S. 584, 593 (1978).

Applying the judicially created exception to the otherwise broad demarcation of statutory subject matter in section 101 can be difficult. *See Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 134-45 (1948) (Frankfurter, J., concurring) ("[S]uch terms as 'the work of nature' and the 'laws of nature' . . . are vague and malleable . . . . Arguments drawn from such terms for ascertaining patentability could fairly be employed to challenge almost every patent."). The analysis is relatively simple if the invention previously existed in nature exactly as claimed. For example, naturally existing minerals, a plant found in the wild, and physical laws such as gravity or E=mc2 are not patentable subject matter, even if they were "discovered" by an enterprising inventor. *Chakrabarty*, 447 U.S. at 309.

Even when an invention does not exist in nature in the claimed state, it may still be directed to subject matter that is not patentable. For example, in *Funk Brothers*, the Supreme Court held a patent to a combination of multiple naturally occurring bacterial strains was not patentable. Although there was "an advantage in the combination," which was apparently "new and useful," none of the bacterial strains "acquire[ed] a different use" in combination. *Funk Bros.*, 333 U.S. at 131-32. The aggregation of the bacterial strains into a single product produced "no new bacteria, no change in the six species of bacteria, and no enlargement of the range of their utility. Each species has the same effect it always had. The bacteria perform in their natural way. . . . They serve the ends nature originally provided and act quite independently of any effort of the patentee." *Id.*

In contrast, the Supreme Court held bacteria that included extra genetic material introduced by the inventor were "a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity 'having a distinctive name, character [and] use'" and therefore patentable. *Chakrabarty*, 447 U.S. at 309-310 (quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887)). *Chakrabarty* explained that there is no distinction between inventions based on living and inanimate objects for the purpose of the patent statute; instead, the "relevant distinction" for the section 101 analysis is "between products of nature . . . and human-made inventions." *Id.* at 312-13. Even if the invention was based on nature, and resulted in a living organism, it may fall within the scope of section 101. For example, "the work of the plant breeder 'in aid of nature' was patentable invention" because "'a plant discovery resulting from cultivation is unique, isolated, and is not repeated by nature, nor can it be reproduced by nature unaided by man.'" *Id.* (quoting S. Rep. No. 315, 71st Cong., 2d Sess., 6-8 (1930)). In *Chakrabarty*, the intervention of man resulted in bacteria with "markedly different characteristics" from nature and "the potential for significant utility," resulting in patentable subject matter. *Id.* at 310.

Funk Brothers and *Chakrabarty* do not stake out the exact bounds of patentable subject matter. Instead, each applies a flexible test to the specific question presented in order to determine whether the claimed invention falls within one of the judicial exceptions to patentability.

Funk Brothers indicates that an invention which "serve[s] the ends nature originally provided" is likely unpatentable subject matter, but an invention that is an "enlargement of the range of . . . utility" as compared to nature may be patentable. 333 U.S. at 131. Likewise, *Chakrabarty* illustrates that an invention with a distinctive name, character, and use, e.g., markedly different characteristics with the potential for significant utility, is patentable subject matter. 447 U.S. at 309-10. Although the two cases result in different outcomes, the inquiry itself is similar.

Courts applied an analogous patentability inquiry long before *Funk Brothers* or *Chakrabarty*. In one notable case, Judge Learned Hand held that purified adrenaline, a natural product, was patentable subject matter. Judge Hand explained that even if the claimed purified adrenaline were "merely an extracted product without change, there is no rule that such products are not patentable." *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95, 103 (S.D.N.Y. 1911). This is because "while it is of course possible logically to call this a purification of the principle" the resulting purified adrenaline was "for every practical purpose a new thing commercially and therapeutically." *Id.* Similarly, in a case applying the Patent Act of 1952,[1] purified vitamin B-12, another natural product, was also held patentable subject matter within the meaning of section 101. *Merck & Co. v. Olin Mathieson Chem. Corp.*, 253 F.2d 156 (4th Cir. 1958). The Fourth Circuit explained that purified vitamin B-12 was "far from the premise of the [naturally occurring] principle. . . . The new product, not just the method, had such advantageous characteristics as to replace the [naturally occurring] liver products. What was produced was, in no sense, an old product." *Id.* at 162-63. These purified pharmaceutical cases are both consistent with Supreme Court precedent: the purified substance was "a new thing . . . therapeutically," *Parke-Davis*, 189 F. at 103, and had such "advantageous characteristics" that what was produced by purification "was, in no sense, an old product." *Merck*, 253 F.2d at 162-63. In other words, the purified natural products were held to have "markedly different characteristics," as compared to the impure products, which resulted in "the potential for significant utility." *Chakrabarty*, 447 U.S. at 310.

In contrast, mere purification of a naturally occurring element is typically insufficient to make it patentable subject matter. For example, our predecessor court held that claims to purified vanadium and purified uranium were not patentable subject matter since these were naturally occurring elements with inherent physical properties unchanged upon purification. *See In re Marden*, 47 F.2d 958, 959 (CCPA 1931) ("[P]ure vanadium is not new in the inventive sense, and, it being a product of nature, no one is entitled to a monopoly of the same."); *In re Marden*, 47 F.2d 957 (CCPA 1931) ("ductile uranium" not patentable because uranium is inherently ductile). Likewise, claims to purified ductile tungsten were not patentable subject matter since pure tungsten existed in nature and was inherently ductile. *General Electric Co. v. De Forest Radio Co.*, 28 F.2d 641, 643 (3d Cir. 1928). In each of these cases, purification did not result in an element with new properties. Instead, the court held the naturally occurring element inherently had the same characteristics and utility (e.g. ductility) as the claimed invention. Consistent with *Funk Brothers* and *Chakrabarty*, the claims all fell within the laws of nature exception.

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[1] The Patent Act of 1952 was the first time patentable subject matter (the current section 101) was separated out from novelty (the current section 102). Previously, these two concepts were combined into a single section.

As illustrated by these examples, courts have long applied the principles articulated in *Funk Brothers* and *Chakrabarty* to different factual scenarios in order to determine whether an invention, as claimed, falls into the laws of nature exception. I see no reason to deviate from this longstanding flexible approach in this case.

II.

We reconsider whether the claims at issue in this case are directed to patentable subject matter following the remand from the Supreme Court in light of its opinion in *Mayo Collaborative Services v.*

Prometheus Laboratories, Inc., 132 S. Ct. 1289 (2012) (*Prometheus*). While the *Prometheus* decision does not control the outcome in this case, it is nonetheless instructive regarding the scope of the law of nature exception. As an initial matter, the *Prometheus* discussion of laws of nature (process claims) clearly ought to apply equally to manifestations of nature (composition claims). Myriad's argument that *Prometheus* is constrained to methods is an untenable position.

As the *Prometheus* court explained: "If a law of nature is not patentable, then neither is a process reciting a law of nature, unless that process has additional features that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself." *Id.* at 1297. *Prometheus* did not, however, overturn *Funk Brothers* or *Chakrabarty*; cases clearly more analogous to the one before us. Using the framework of *Funk Brothers* and *Chakrabarty* in conjunction with the direction of *Prometheus*, the applicable principles are: (1) laws of nature/manifestations of nature are not patentable; (2) a composition of matter with "markedly different characteristics" from that found in nature with the potential for significant utility is directed to patentable subject matter.

Does the isolation process change the DNA from an unpatentable manifestation of nature into a patentable composition of matter? *Id.* at 1299. Does the claimed isolated DNA have markedly different characteristics with the potential for significant utility, e.g., an "enlargement of the range of . . . utility" as compared to nature? *Chakrabarty*, 447 U.S. at 309-310; *Funk Bros.*, 333 U.S. at 131.

The isolated DNA claims of the patents in suit fall into two categories. The first category of claims is directed to isolated sequences that are identical to naturally occurring gene sequences. These include claims encompassing both the isolated full length gene sequence (e.g. claim 1 of '282 patent), which are thousands of nucleotides, and claims to shorter isolated DNA strands, with as few as fifteen nucleotides, whose nucleotide sequence is found on the chromosome (e.g. claim 5 of '282 patent). The second category of claims is directed to isolated DNA sequences that are different from the naturally occurring gene sequences. These include claims to isolated cDNA molecules (e.g. claim 2 of the '282 patent), which differ from the natural gene sequence in that the introns are removed, and are the opposite (complementary) sequence of the naturally occurring RNA.

The cDNA claims present the easiest analysis. Although the plaintiffs (now plaintiff) in the suit argue, and the district court held, that cDNA falls within the "laws of nature" exception to section 101 patentability, the claimed cDNA sequences do *not* exist in nature. Moreover, since cDNA has all of the introns removed, and only contains the coding nucleotides, it can be used to express a protein in a cell which does *not* normally produce it. Of course, the claimed isolated cDNA is inspired by nature—after all naturally occurring RNA is the template upon which cDNA is constructed. Because it is used as a template, however, cDNA has a complementary sequence of nucleotides, and therefore has a *completely different* nucleotide sequence than the RNA. Moreover, DNA has a different chemical structure than RNA, including a different base (T instead of U, respectively) and sugar units (deoxyribose instead of ribose, respectively). This results in, among other things, greater stability for the DNA sequence as compared to the RNA sequence.

cDNA sequences thus have a distinctive character and use, with markedly different chemical characteristics from either the naturally occurring RNA or any continuous DNA sequence found on the chromosome. The claimed isolated cDNA sequences are the creation of man, made using biological tools and the naturally occurring mRNA as a template. cDNA is therefore not one of the "'manifestations of . . . nature, free to all men and reserved exclusively to none'" that falls outside of the patent system. *Chakrabarty*, 447 U.S. at 309 (quoting *Funk Bros.*, 333 U.S. at 130). I decline to extend the laws of nature exception to reach entirely manmade sequences of isolated cDNA, even if those sequences are inspired by a natural template. I therefore join the majority opinion with respect to the claims to cDNA sequences.[2]

DNA sequences that have the same pattern of DNA bases as a natural gene, in whole or in part, present a more difficult issue. Unlike the isolated cDNA molecules, whose sequence is not present in nature, the isolated DNA claims include nucleotide sequences which are found in the human body, albeit as part of a much larger molecule, the chromosome. To the extent the majority rests its conclusion on the chemical differences between genomic and isolated DNA (breaking the covalent bonds), I cannot agree that this is sufficient to hold that the claims to human genes are directed to patentable subject matter. I agree that isolated genes are a different molecule and are therefore not squarely analogous to unpatentable minerals, created by nature without the assistance of man. The claimed isolated DNA molecules, which are truncations (with different ends) of the naturally occurring DNA found as part of the chromosome in nature, are not naturally produced without the intervention of man.

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[2] To the extent the claims to shorter portions of cDNA include only naturally occurring sequences found in the chromosome, for example claim 6 of the '282 patent, my reasoning is the same as for the isolated sequences of claim 5, discussed below.

I begin with the short isolated sequences such as those covered by claim 5 which is directed to "an isolated DNA having at least 15 nucleotides of the DNA of claim 1." This claim covers a sequence as short as 15 nucleotides and arguably as long as the entire gene. For this claim to be patent eligible, all of the sequences ranging from the 15 nucleotide sequence to the full gene must be patentable subject matter. The shorter isolated DNA sequences have a variety of applications and uses in isolation that are new and distinct as compared to the sequence as it occurs in nature. For example, these sequences can be used as primers in a diagnostic screening process to detect gene mutations. These smaller isolated DNA sequences—including isolated radiolabeled sequences mirroring those on the chromosome—can also be used as the basis for probes. Naturally occurring DNA cannot do this. Unlike the isolated DNA, naturally occurring DNA simply does not have the requisite chemical and physical properties needed to perform these functions.

The ability to use isolated DNA molecules as the basis for diagnostic genetic testing is clearly an "enlargement of the range of . . . utility" as compared to nature. *Funk Bros.*, 333 U.S. at 131. In *Prometheus*, the Supreme Court held that the claims at issue were not directed to patentable subject matter because they merely "set forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm." 132 S. Ct. at 1296-97. The claimed relationship was "a consequence of the ways in which thiopurine compounds are metabolized by the body—entirely natural processes." *Id.* at 1297.

There is no suggestion that the human body naturally uses 15-mers as primers to synthesize DNA, or that the attendant process of "probing" a patient's DNA to detect a mutation is somehow a natural law. The ability to use a short strand of DNA as a primer or probe to determine whether a patient has a mutation is a new and important utility substantially different from the role of that DNA as it occurs in nature. Indeed, many of the plaintiffs in this case submitted declarations indicating that they wanted to either offer such testing or receive such testing. Unlike *Prometheus*, the claims to short isolated strands of DNA are not directed to the relationship between the mutation and cancer, but rather to a new tool that can be used to determine if that relationship exists. The short isolated DNA sequences have markedly different properties which are directly responsible for their new and significant utility. *Chakrabarty*, 447 U.S. at 309-10. It is not the chemical change alone, but that change combined with the different and beneficial utility that leads me to conclude that small isolated DNA fragments are patentable subject matter. *Id.* at 310.

In fact, much of the dissent's analysis with regard to the full gene would seem to support my conclusion that small isolated DNA molecules are directed to patent-eligible subject matter. The dissent explains why the baseball bat is directed to patent eligible subject matter: "man has defined the parts that are to be retained and the parts that are to be discarded, and he has molded the retained portion into a product that bears little resemblance to that which occurs naturally." Dissent at 11-12. The exact same thing is true with regard to primer and probe claims. Man has whittled the chromosomal DNA molecule down to a 15 nucleotide sequence – defining the parts to be retained and discarded.[3] And the result is a product with a function (primer or probe) that is entirely different from the full gene from which it was obtained.[4] I conclude that the small, isolated DNA molecules are an alteration of the natural product "with markedly different characteristics from any found in nature and one having the potential for significant utility." 447 U.S. at 310.

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[3] If adding functionality to a naturally occurring molecule, for example adding a lipid chain, is a creation of man then removing functionality, for example truncating a natural DNA sequence or protein to yield smaller molecules with new properties should also be. In either case, it is the intervention of man that created a new molecule. After all, the hand of man is just as apparent in the David, created by removing stone from a block of marble, as the ceiling of the Sistine Chapel, created by adding layers of paint to an existing structure.

[4] The dissent analogizes the full BRCA gene to a slab of marble found in the earth as distinct from the sculpture carved into it – which the dissent indicates would be worthy of intellectual property protection. If the multi-thousand nucleotide BRCA gene is the slab, isn't the 15 nucleotide primer the sculpture?

Turning now to the longer strands of isolated DNA, isolated strands which include most or all of the gene present a more difficult case. Some of the claims at issue, for example '282 patent claim 5, are genus claims, drafted broadly enough to include both short fragments as well as the entire isolated gene sequence. While I ultimately conclude that these longer isolated sequences, including the isolated gene sequence as a whole, are also patentable subject matter, I do so for a reason different than for the shorter sequences.

All of the same structural arguments apply to any length of isolated DNA so, like the shorter strands, an isolated DNA coding for a gene does have a literal chemical difference from the gene as it appears on the chromosome. Unlike the shorter strands of isolated DNA, the chemical and structural differences in the isolated gene do not clearly lead to an "enlargement of the range of . . . utility" as compared to nature. *Funk Bros.*, 333 U.S. at 131. For example, the full length gene is too large to be used as a probe. *See* J.A. 4322 (a probe is a DNA molecule usually 100-1,000 bases long). Likewise, an entire isolated gene appears unsuitable for use as a primer in genetic screening for mutations in that same gene. *See* J.A. 4323 (Primers "are complementary to an exact location of a much larger target DNA molecule."). The isolated full length gene does not clearly have a new utility and appears to simply serve the same ends devised by nature, namely to act as a gene encoding a protein sequence.

If I were deciding this case on a blank canvas, I might conclude that an isolated DNA sequence that includes most or all of a gene is not patentable subject matter. The scope of the law of nature/manifestation of nature exception was certainly enlarged in *Prometheus*. But we do not decide this case on a blank canvas. Congress has, for centuries, authorized an expansive scope of patentable subject matter. Likewise, the United States Patent Office has allowed patents on isolated DNA sequences for decades, and, more generally, has allowed patents on purified natural products for centuries. There are now thousands of patents with claims to isolated DNA, and some unknown (but certainly large) number of patents to purified natural products or fragments thereof.[5] As I explain below, I believe we must be particularly wary of expanding the judicial exception to patentable subject matter where both settled expectations and extensive property rights are involved.[6]

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[5] See, e.g., U.S. Patent 3,067,099 (claiming vancomycin, an antibiotic produced by bacteria found in soil) and U.S. Patent 4,552,701 (claiming a vancomycin fragment produced by removing a sugar unit). A natural product fragment, for example a naturally occurring antibiotic with a sugar moiety removed, is highly analogous to isolated DNA. In each case, the claimed molecule is a smaller fragment of a naturally occurring molecule, with some naturally occurring functionality removed. See U.S. Patent 4,552,701, col.3-4 (compare entry 2 with entries 10 and 13).

[6] My analysis of the claims at issue assumes that they do not include an isolated, full length chromosome. I do not believe that a claim to an entire chromosome, for example chromosome

III.

For more than a decade the Patent Office's policy has been that "[a]n isolated and purified DNA molecule that has the same sequence as a naturally occurring gene is eligible for a patent because . . . that DNA molecule does not occur in that isolated form in nature . . . ." 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001). I do not agree with the dissent's characterization of the PTO position as perfunctory. The PTO concluded that isolated DNA is patentable because it is different from what is found in nature – the process of synthesizing it or isolating it changes it. While the PTO lacks substantive rule making authority, it is not without expertise in this area. The explicit statement of the Patent Office's position on isolated DNA, however, is simply a continuation of a longstanding and consistent policy of allowing patents for isolated natural products. *See id.* (noting U.S. Patent 141,072, claiming "[y]east, free from organic germs of disease," issued to Louis Pasteur in 1873); *cf. In re Bergstrom*, 427 F.2d 1394 (CCPA 1970) (isolated prostaglandins patentable). According to the Patent Office, isolated DNA is no different from the isolated natural products of *Parke-Davis*. *See* 66 Fed. Reg. at 1093 (quoting *Parke-Davis*).

Even before the current guidelines formalized the Patent Office's position, it granted patents to human

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17, is patentable subject matter. First, there is no indication that the chromosome in isolation has markedly different characteristics compared to the chromosome in nature. Second, unlike claims to isolated genes, there is no indication of either settled expectations or extensive property rights for claims to isolated chromosomes. This is undoubtedly due to the small number of chromosomes as compared to the number of genes.

genes in the early 1980s, and subsequently issued thousands of patents on "isolated DNA." Majority at 54. In fact, claims similar to the ones at issue in this case have been the focal point of important litigation. For example, *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200 (Fed. Cir. 1991) involved a claim to "'[a] purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.'" *Id.* at 1203-04 (quoting U.S. Patent No. 4,703,008, claim 2). We affirmed that this claim was valid and infringed. *Id.* at 1219. Erythropoietin, also known as EPO, went on to become the biggest-selling biotechnology drug developed to that point, resulted in billions of dollars in sales, and accounted for over 50% of Amgen's revenue in 1997. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F.Supp.2d 69, 77 (D. Mass. 2001). Isolated DNA claims, at least in the case of Amgen, represent crucial and exceedingly valuable property rights.

The settled expectations of the biotechnology industry – not to mention the thousands of issued patents – cannot be taken lightly and deserve deference. This outpouring of scientific creativity, spurred by the patent system, reflects a substantial investment of time and money by the biotechnology industry to obtain property rights related to DNA sequences. The type of fundamental alteration in the scope of patentable subject matter argued in this case "risk[s] destroying the legitimate expectations of inventors in their property." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002). I believe leaving intact the settled expectations of property owners is particularly important in light of the large number of property rights involved, both to isolated DNA and to purified natural products generally.

The Supreme Court has warned that "courts must be cautious before adopting changes that disrupt the settled expectations of the inventing community." *Id.* at 739. The settled expectations of the inventing community with respect to isolated DNA claims are built upon the broad language of the statute, judicial precedent, such as *Parke-Davis* and *Merck*, and the Patent Office's longstanding policy and practice. Neither *Funk Brothers* nor *Chakrabarty* purported to overrule either the early cases or the Patent Office's practice; indeed, as discussed *supra*, these cases weigh the same considerations as *Parke-Davis* and *Merck*. "'To change so substantially the rules of the game now,'" after more than a century of practice, "'could very well subvert the various balances the PTO sought to strike when issuing the numerous patents which have not yet expired and which would be affected by our decision.'" *Festo*, 535 U.S. at 739 (quoting *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 32 n.6 (1997)).

Although the Patent Office has consistently followed the same policy for a decade (and arguably a century or more), the United States, as an amicus, now argues that the Patent Office's published guidelines are incorrect and a misstatement of the law. In place of these guidelines, the government suggested that a "magic microscope" would provide a useful metaphor for guiding our section 101 analysis. The magic microscope, however, would not see the claimed DNA molecules at issue in this case. An isolated DNA molecule has different chemical bonds as compared to the "unisolated" sequence in the chromosome (the ends are different). In short, the claimed molecules cannot be seen in nature through the magic microscope. While you may be able to see the order of DNA nucleotides in the chromosome, the isolated fragment of DNA is a different molecule. Creating the claimed isolated DNA sequences therefore results in a distinctly unnatural molecule.[7] Even the dissent agrees that the isolated DNA molecules at issue require cleaving chemical bonds, though it disputes the importance of the resulting distinct "'molecular species.'" Dissent at 7 (quoting Linus Pauling, *The Nature of the Chemical Bond* 6 (3d ed. 1960)).

The dissent claims that the Patent Office's past views are "substantially undermined by the position the government has taken in this case." Dissent at 20. The Patent Office's prior practice, however, is particularly important since it resulted in a large number of property rights over the past decades. If the government decided to change course in the

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[7] This also illustrates why the government's analogies to situations dealing with elements, for example lithium, are inapposite. Even assuming the government's contention that lithium does not currently exist in isolated form in nature, it is nevertheless clear that elemental lithium, a basic building block provided by nature, at some point must have reacted with, e.g., water to form the naturally occurring lithium salts. In contrast, an isolated DNA sequence did not necessarily exist before reacting further to produce the corresponding naturally occurring chromosomal DNA. Unlike a lithium salt, the chromosome does not imply that an isolated DNA molecule of 15 nucleotides – or even a gene – necessarily previously existed as an isolated molecule in nature.

Patent Office, and decline to issue new patents to isolated genes, it would not impact these existing property rights. This, however, is not what the government argues in this case. Instead the government argues for an entirely different interpretation of the law that would destroy existing property rights. Although the dissent points out that *Chakrabarty* overturned the Patent Office's practice of denying patents to microorganisms, there is a clear difference between allowing additional patent protection where none previously existed, and denying patent protection decades (or centuries) after the fact, thereby eliminating a large number of property rights. *Chakrabarty*, consistent with the broad language of the statute, allowed additional patents where none previously existed. In contrast, the government proposes to destroy existing property rights based on a judge made exception to that same broad language. This is a dramatic step that I believe is best left to the Congress.

Nevertheless, the government claims that "this is a pure question of law" and that we can therefore feel free to ignore the years of Patent Office practice and the accompanying expectations that practice created within the industry. The government argues that we should not defer to the broad language (all but unchanged since 1793) provided by Congress in the patent statute, or allow Congress to decide whether it is necessary to correct the Patent Office's practice through legislation. It is tempting to use our judicial power in this fashion, especially when the patents in question raise substantial moral and ethical issues related to awarding a property right to isolated portions of human DNA – the very thing that makes us humans, and not chimpanzees.

The invitation is tempting, but I decline the opportunity to act where Congress has chosen not to. Congress at least implicitly approved of the Patent Office's policy of awarding patents on genes and DNA sequences. For example, Congress included, as part of the Patent Office's appropriations, language affirming the Patent Office's interpretation of section 101 to prohibit patents on human organisms. Consolidated Appropriations Act, 2004, Pub. L. No. 108-199, § 634, 118 Stat. 3, 101. Although Congress was aware "that there are many institutions . . . that have extensive patents on human genes," 149 Cong. Rec. H7248, H7274, it explicitly declined to implement legislation to "affect any of those current existing patents." 149 Cong. Rec. E2417-01. To the contrary, it made clear that the language related to "human organisms" was not intended to change the Patent Office's policy with respect to claims to genes, stem cells, or other similar inventions.[8] Far from oblivious to the patenting of genes, Congress introduced and declined to pass several bills which would put a moratorium on gene patents,[9] authorize funding for the study of whether genes ought to be patentable,[10] and exempt from patent infringement anyone who uses patented genes for non-commercial research purposes or medical practitioners who use genetic diagnostic tests.[11] Congress is obviously aware of the issues presented in this case and I believe "[a]ny recalibration of the standard of [patentability] remains in its hands." Microsoft Corp. v. i4i Ltd., 131 S. Ct. 2238, 2252 (2011).

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[8] "What I want to point out is that *the U.S. Patent Office has already issued patents on genes*, stem cells, animals with human genes, and a host of non-biologic products used by humans, but it has not issued patents on claims directed to human organisms, including human embryos and fetuses. *My amendment would not affect the former*, but would simply affirm the latter." 149 Cong. Rec. E2417-01 (emphasis added); *see also* 157 Cong. Rec. E1177-04 (resubmitting this testimony in the context of the current patent reform legislation).

[9] At least one bill was introduced in Congress to put a moratorium on patents to human genes or gene sequences. *See, e.g.*, The Animal and Gene Patent Moratorium Bill (S.387 1993).

The judiciary cannot engage in an *ad hoc* innovation-based analysis, which is why the exceptions to patentability apply only to the clearest cases: a new mineral discovered in the earth, or a new plant found in the wild, or E=mc2, or the law of gravity. It is Congress, with "the constitutional authority and the institutional ability to accommodate fully the varied permutations of competing interests that are inevitably implicated by such new technology," *Sony Corp. of America v. Universal City Studios, Inc.*, 464 U.S. 417, 431 (1984), who must decide whether it is necessary to change the scope of section 101 to exclude the kind of isolated DNA claims at issue here. It is not clear to me that *Chakrabarty*, *Funk Brothers*, or *Prometheus* leads inexorably to the conclusion that isolated DNA molecules are not patentable subject matter. I decline the invitation to broaden the law of nature exception.

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[10] The Genomic Science and Technology Innovation Act of 2002 (H.R. 3966).

[11] The Genomic Research and Diagnostic Accessibility Act of 2002 (H.R. 3967). As the bill's sponsor explained: "It is important to note that this section would not overturn the commercial rights of patent holders. If a research [organization] utilizing the exemption makes a commercially viable finding, he or she would still have to negotiate any rights to market the new discovery with the patent holder." 148 Cong. Rec. E353-03.

Given the complicated technology and conflicting incentives at issue here, any change must come from Congress. *See Gottschalk v. Benson*, 409 U.S. 63, 72-73 (1972) (A section 101 analysis raises "considerable problems . . . which only committees of Congress can manage, for broad powers of investigation are needed, including hearings which canvass the wide variety of views which those operating in this field entertain. The technological problems tendered [by the parties] . . . indicate to us that considered action by the Congress is needed.").

IV.

"The rule that the discovery of a law of nature cannot be patented rests . . . on the . . . fundamental understanding that they are not the kind of 'discoveries' that the statute was enacted to protect." *Flook*, 437 U.S. at 593. Is an isolated kidney patentable? Probably not, but as far as I can tell nobody ever thought isolating organs from someone's body was the kind of discovery "that the statute was enacted to protect." In contrast, purifying or isolating natural products has historically been exactly the kind of discovery protected by the patent statutes. There is a century-long history of affirming patent protection for isolated and purified biological products ranging from hormones to vitamins to proteins to antibiotics. These inventions must have seemed miraculous at the time, providing previously unknown therapeutic options to treat sickness. The fact that these molecules might have existed in nature did not foreclose patent protection in view of the extraordinary benefits accessible to man after isolation.

The Patent Office has, for more than a decade, affirmatively stated its belief that isolated DNA is patentable for the same reasons as isolated vitamins or hormones. There is no indication from Congress that this view is wrong; to the contrary, it appears Congress also believes DNA is patentable. This long-term policy of protecting isolated DNA molecules has resulted in an explosion of innovation in the biotechnology industry, an industry which, unlike the financial services industry or even the software industry, depends on patents to survive. Holding isolated DNA not patentable would destroy long settled industry expectations for no reason other than a gut feeling that DNA is too close to nature to be patentable, an arbitrary decision based on a judge-made exception. I believe that isolated DNA fragments, which have both chemical changes from the naturally occurring genomic DNA as well as new utility, are "the kind of 'discoveries' that the statute was enacted to protect." I therefore decline to extend the "laws of nature" exception to include isolated DNA sequences.

This case typifies an observation by the late Chief Judge Markey, our first Chief Judge, that "[o]nly God works from nothing. Men must work with old elements." *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 n.3 (Fed. Cir. 1985) (quotation, citations omitted). Human DNA is, for better or worse, one of the old elements bequeathed to men to use in their work. The patents in this case revealed a new molecular understanding about ourselves; "the inventions most benefiting mankind are those that 'push back the frontiers of chemistry, physics, and the like.'" *Chakrabarty*, 447 U.S. at 316 (quoting *Great A.&P. Tea Co. v. Supermarket Corp.*, 340 U.S. 147, 154 (1950)). We cannot, after decades of patents and judicial precedent, now call human DNA fruit from the poisonous tree, and punish those inquisitive enough to investigate, isolate, and patent it. "Our task . . is the narrow one of determining what Congress meant by the words it used in the statute; once that is done our powers are exhausted." *Id.* at 318. This inquiry does not have moral, ethical, or theological components. *Cf. id.* at 316-17 ("[W]e are without competence to entertain" arguments about "the grave risks" generated by genetic research.). "The choice we are urged to make is a matter of high policy for resolution within the legislative process after the kind of investigation, examination, and study that legislative bodies can provide and courts cannot." *Id.* at 317. The patents in this case might well deserve to be excluded from the patent system, but that is a debate for Congress to resolve. I will not strip an entire industry of the property rights it has invested in, earned, and owned for decades unchallenged under the facts of this case.

United States Court of Appeals for the Federal Circuit

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, THE AMERICAN COLLEGE OF MEDICAL GENETICS, THE AMERICAN SOCIETY FOR CLINICAL PATHOLOGY, THE COLLEGE OF AMERICAN PATHOLOGISTS, HAIG KAZAZIAN, MD, ARUPA GANGULY, PHD, WENDY CHUNG, MD, PHD, HARRY OSTRER, MD, DAVID LEDBETTER, PHD, STEPHEN WARREN, PHD, ELLEN MATLOFF, M.S., ELSA REICH, M.S., BREAST CANCER ACTION, BOSTON WOMEN'S HEALTH BOOK COLLECTIVE, LISBETH CERIANI, RUNI LIMARY, GENAE GIRARD, PATRICE FORTUNE, VICKY THOMASON, AND KATHLEEN RAKER,

Plaintiffs-Appellees,

v.

UNITED STATES PATENT AND TRADEMARK OFFICE,

Defendant,

and

MYRIAD GENETICS, INC.,

Defendant-Appellant,

and

LORRIS BETZ, ROGER BOYER, JACK BRITTAIN, ARNOLD B. COMBE, RAYMOND GESTELAND, JAMES U. JENSEN, JOHN KENDALL MORRIS, THOMAS PARKS, DAVID W. PERSHING, AND

MICHAEL K. YOUNG, IN THEIR OFFICIAL
CAPACITY AS DIRECTORS OF THE UNIVERSITY
OF UTAH RESEARCH FOUNDATION,

Defendants-Appellants.

2010-1406

Appeal from the United States District Court for the Southern District of New York in case No. 09-CV-4515, Senior Judge Robert W. Sweet.

BRYSON, *Circuit Judge*, concurring in part and dissenting in part:

I concur with the portions of this court's judgment that are directed to standing, the patentability of the cDNA claims, and the patentability of the method claims. I respectfully dissent from the court's holding that Myriad's BRCA gene claims and its claims to gene fragments are patent-eligible. In my view, those claims are not directed to patentable subject matter, and the court's decision, if sustained, will likely have broad consequences, such as preempting methods for whole-genome sequencing, even though Myriad's contribution to the field is not remotely consonant with such effects.

In its simplest form, the question in this case is whether an individual can obtain patent rights to a human gene. From a commonsense point of view, most observers would answer, "Of course not. Patents are for inventions. A human gene is not an invention." The essence of Myriad's argument in this case is to say that it has not patented a human gene, but something quite different—an *isolated* human gene, which differs from a native gene because the process of extracting it results in changes in its molecular structure (although not in its genetic code). We are therefore required to decide whether the process of isolating genetic material from a human DNA molecule makes the isolated genetic material a patentable invention. The court concludes that it does; I conclude that it does not.

At the outset, it is important to identify the inventive contribution underlying Myriad's patents. Myriad was not the first to map a BRCA gene to its chromosomal location. That discovery was made by a team of researchers led by Dr. Mary-Claire King. *See* Jeff M. Hall et al., *Linkage of Early-Onset Familial Breast Cancer to Chromosome 17q21*, 250 Science 1684 (1990). And Myriad did not invent a new method of nucleotide sequencing. Instead, it applied known sequencing techniques to identify the nucleotide order of the BRCA genes.[1] Myriad's discovery of those sequences entailed difficult work, and the identified sequences have had important applications in the fight against breast cancer. But the discovery of the sequences is an unprotectable fact, just like Dr. King's discovery of the chromosomal location of the BRCA1 gene.

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[1] There is some dispute over whether other inventors helped Myriad discover the BRCA sequences or discovered the BRCA2 sequence before Myriad. Because those disputes are irrelevant to the question of patentable subject matter, I refer to the discovery of the BRCA sequences as Myriad's work.

Of course, Myriad is free to patent applications of its discovery. As the first party with knowledge of the sequences, Myriad was in an excellent position to claim applications of that knowledge. Many of its unchallenged claims are limited to such applications. *See, e.g.*, '441 patent, claim 21; '492 patent, claim 22; '282 patent, claim 9. Yet some of Myriad's challenged composition claims effectively preempt any attempt to sequence the BRCA genes, including whole-genome sequencing. In my view, those claims encompass unpatentable subject matter, and a contrary ruling is likely to have substantial adverse effects on research and treatment in this important field.

I

As the majority and concurring opinions explain, the DNA claims at issue in this case fall into three categories: claims that cover the isolated BRCA genes (claim 1 of the '282 patent, claim 1 of the '473 patent, and claims 1 and 6 of the '492 patent); claims that cover only the BRCA cDNA (claims 2 and 7 of the '282 patent and claim 7 of the '492 patent); and claims that cover portions of the BRCA genes and cDNA as small as 15 nucleotides long (claims 5 and 6 of the '282 patent). I first address the claims to the BRCA genes.

A

In the seminal case of *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), the Supreme Court held that an artificial life form could be patented. In the course of its opinion, and critically for purposes of its reasoning, the Court stated that not all living things or other items found in nature were subject to patenting. The Court explained that although the language of section 101 of the Patent Act is broad, it is not the case that it "has no limits or that it embraces every discovery." *Id.* at 309. The Court then set forth the general proposition that "laws of nature, physical phenomena, and abstract ideas have been held not patentable." *Id.* As examples, the Court noted that "a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter." Thus, even though a mineral or a plant is a "composition of matter," and could be viewed as falling within a broad construction of section 101, the Court explained that those "manifestations of . . . nature" are not patentable subject matter, but are "free to all men and reserved exclusively to none." *Id.*, quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948); *see also Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010).

The Court in *Chakrabarty* held the artificial life form at issue in that case to be patentable because the claim was "not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity 'having a distinctive name, character [and] use.'" 447 U.S. at 309-10, quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887). In distinguishing between naturally occurring substances and nonnaturally occurring manufactures, the Court relied heavily on its earlier decision in *Funk Brothers*, in which the inventor discovered that certain useful bacterial strains did not exert an inhibitive effect on one another. Based on that discovery, the inventor obtained a patent on a mixed culture of those non-inhibitive strains. The Supreme Court held the product unpatentable, however, because the bacteria remained structurally and functionally the same as in their natural state. *Funk Bros.*, 333 U.S. at 131. By contrast, because Chakrabarty had produced "a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility," the Court held Chakrabarty's invention to be patentable. *Chakrabarty*, 447 U.S. at 310.

B

Myriad's claims to the isolated BRCA genes seem to me to fall clearly on the "unpatentable" side of the line the Court drew in *Chakrabarty*. Myriad is claiming the genes themselves, which appear in nature on the chromosomes of living human beings. The only material change made to those genes from their natural state is the change that is necessarily incidental to the extraction of the genes from the environment in which they are found in nature. While the process of extraction is no doubt difficult, and may itself be patentable, the isolated genes are not materially different from the native genes. In this respect, the genes are analogous to the "new mineral discovered in the earth," or the "new plant found in the wild" that the Supreme Court referred to in *Chakrabarty*. It may be very difficult to extract the newly found mineral or to find, extract, and propagate the newly discovered plant. But that does not make those naturally occurring items the products of invention.

The same is true for human genes. Like some minerals, they are hard to extract from their natural setting. Also like minerals, they can be used for purposes that would be infeasible if they remained in their natural setting. And the process of extracting minerals, or taking cuttings from wild plants, like the process of isolating genetic material, can result in some physical or chemical changes to the natural substance. But such changes do not make extracted minerals or plant cuttings patentable, and they should not have that effect for isolated genes. In each case, merely isolating the products of nature by extracting them from their natural location and making those alterations that are attendant to their extraction does not give the extractor the right to patent the products themselves.

The majority characterizes the isolated genes as new molecules and considers them different substances from the corresponding native DNA.[2] Because the native BRCA genes are chemically bonded to other genes and histone proteins, the majority concludes that cleaving those bonds to isolate the BRCA genes turns the isolated genes into "different materials." Yet there is no magic to a chemical bond that requires us to recognize a new product when a chemical bond is created or broken, but not when other atomic or molecular forces are altered.[3] A chemical bond is merely a force between two atoms or groups of atoms strong enough "to make it convenient for the chemist to consider [the aggregate] as an independent molecular species." Linus Pauling, *The Nature of the Chemical Bond* 6 (3d ed. 1960). Weaker interatomic forces will be broken when, for example, a dirty diamond is cleaned with water or another solvent, but that does not make the clean diamond a human-made invention. *See Am. Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1, 12 (1931) (cleaning a shell by acid and then grinding off a layer with an emery wheel did not convert it into a different product). Nor should it make a difference for purposes of patentability if the portion of a wild plant that is collected for purposes of later regeneration is separated from the original plant by chemical means or by scissors.

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[2] Although I recognize that Judge Lourie and Judge Moore, while reaching the same ultimate conclusions, have taken analytical paths that differ in some respects, for convenience I will refer to Judge Lourie's opinion as the majority opinion and Judge Moore's opinion as the concurring opinion.

[3] The majority characterizes the question in this case as turning on the breaking of covalent bonds linking the BRCA genes to the rest of the DNA in chromosomes 13 and 17, but its analysis appears to place patentable weight on the breaking of other chemical bonds, such as the hydrogen bonds that are broken when separating DNA from histones or—in an example

If the changes in the DNA molecule that occur as part of the process of isolation render the gene claims patentable, the same analysis would seem to apply to chemical elements that do not appear in their atomic form in nature. For example, isolated lithium does not occur naturally because it reacts with air and water and thus is found in nature only as part of a chemical compound, ionically bound to other elements. Robert E. Krebs, *The History and Use of Our Earth's Chemical Elements* 48 (2d ed. 2006). Once isolated, lithium has many industrial applications, and in order to isolate lithium, it is necessary to break ionic bonds in the lithium

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unrelated to this case—the ionic bonds that are broken when lithium is derived from a salt. It is difficult to see why differences between types of chemical bonds should matter for patentability purposes, and I see little support for such a distinction in the governing precedents.

compounds that are found in nature. But it seems plain that elemental lithium (like other elements) would not be patentable subject matter, even if it could only be extracted from nature through an isolation process.

The principles underlying that analysis apply to genetic material as well. In order to isolate the BRCA gene, it is necessary to break chemical bonds that hold the gene in its place in the body, but the genetic coding sequence that is the subject of each of the BRCA gene claims remains the same whether the gene is in the body or isolated. If we are to apply the conventional nomenclature of any field to determine whether Myriad's isolated DNA claims are "new," it would seem to make more sense to look to genetics, which provides the language of the claims, than to chemistry. Aside from Myriad's cDNA claims, its composition claims are not defined by any particular chemical formula. For example, claim 1 of the '282 patent covers all isolated DNAs coding for the BRCA1 protein, with the protein being defined by the amino acid sequence encoded by the naturally occurring BRCA1 gene. From a molecular perspective, that claim covers a truly immense range of substances from the cDNA that is 5,914 nucleotides long to the isolated gene that contains more than 120,000 nucleotides. And the patent does not define the upper end of that range because the patent does not identify a unique nucleotide sequence for the 120,000-nucleotide-long isolated BRCA1 gene. Instead, the patent contains a sequence that is just 24,000 nucleotides long with numerous gaps denoted "vvvvvvvvvvvvvv." '282 patent, fig. 10. An almost incalculably large number of new molecules could be created by filling in those gaps with almost any nucleotide sequence, and all of those molecules would fall within the scope of claim 1. Included in that set are many important molecular variations to the BRCA1 gene that Myriad had not yet discovered and could not have chemically described. Yet those molecules would share only one unifying characteristic: each would code for the same protein as the naturally occurring BRCA1 gene.

From a genetic perspective, that claim covers one "composition of matter"—the BRCA1 gene. The isolated BRCA genes are identical to the BRCA genes found on chromosomes 13 and 17. They have the same sequence, they code for the same proteins, and they represent the same units of heredity. It is true that the claimed molecules have been cleaved and that they possess terminal groups that differ from those found on naturally occurring genes. The majority attaches significance to those facts. But the function of the isolated DNA molecules is attributable not to the nature of the isolation process or to the identity of the terminal groups on the molecules; the function of the claimed molecules is dictated by the nucleotide sequence of the gene—a sequence that is determined by nature and that appears in nature exactly as it appears in the claimed isolated DNA. During the transcription phase of protein synthesis, the BRCA genes are separated from chromosomal proteins. The transcription process then proceeds from a starting point called the promoter to a stopping point often called the terminator. James D. Watson et al., *Molecular Biology of the Gene* 382, 394-96 (6th ed. 2008). The only difference between the naturally occurring BRCA genes during transcription and the claimed isolated DNA is that the claimed genes have been isolated according to nature's predefined boundaries, i.e., at points that preserve the ability of the gene to express the protein for which it is coded.

In that respect, extracting a gene is akin to snapping a leaf from a tree. Like a gene, a leaf has a natural starting and stopping point. It buds during spring from the same place that it breaks off and falls during autumn. Yet prematurely plucking the leaf would not turn it into a human-made invention. *See Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282, 1295 (Fed. Cir. 2010) (Dyk, J., concurring in part and dissenting in part). That would remain true if there were minor differences between the plucked leaf and the fallen autumn leaf, unless those differences imparted "markedly different characteristics" to the plucked leaf. *Chakrabarty*, 447 U.S. at 310.

Another example underscores the problem with characterizing the isolated gene as a patentable invention. A human kidney is a product of nature; it does not become a patentable invention when it is removed from the body, even if the patentee has developed an improved procedure for extracting the kidney, and even if the improved procedure results in some physical or chemical changes to the kidney at the points where the kidney was attached to the host body. But if that is so, then why should an isolated gene be treated differently for purposes of section 101? While the isolation of a gene involves the alteration of a single molecule, it is difficult to accept that it should make a difference, for purposes of patentability, whether the isolated substance is part of a single molecule, as in the case of the BRCA genes, or part of a very large aggregation of molecules, as in the case of a kidney.

Both the majority and the concurring opinions attach significant weight to the fact that the claimed coding portions of the native BRCA genes are part of a much larger molecule and that the isolated BRCA genes, being smaller molecules extracted from the larger one, are therefore man-made inventions. But to argue that the isolated BRCA gene is patentable because in its native environment it is part of a much larger structure is no more persuasive than arguing that although an atom may not be patentable, a subatomic particle is patentable because it was previously part of a larger structure, or that while a tree is not patentable, a limb of the tree becomes a patentable invention when it is removed from the tree.

Of course, it is an oversimplification to say that something that can be characterized as "isolated" or "extracted" from its natural setting always remains a natural product and is not patentable. One could say, for example, that a baseball bat is "extracted" or "isolated" from an ash tree, but in that case the process of "extracting" the baseball bat necessarily changes the nature, form, and use of the ash tree and thus results in a manmade manufacture, not a naturally occurring product. In that setting, man has defined the parts that are to be retained and the parts that are to be discarded, and he has molded the retained portion into a product that bears little resemblance to that which occurs naturally. The result of the process of selection is a product with a function that is entirely different from that of the raw material from which it was obtained. In the case of the BRCA genes, by contrast, nature has defined the genes as independent entities by virtue of their capacity for protein synthesis and, ultimately, trait inheritance. Biochemists extract the target genes along lines defined by nature so as to preserve the structure and function that the gene possessed in its natural environment. In such a case, the extraction of a product in a manner that retains the character and function of the product as found in nature does not result in the creation of a human invention.[4] That principle was captured by the Supreme Court's statement in *Chakrabarty* that the invention in that case was not to "a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter 'having a distinctive name, character [and] use.'" 447 U.S. at 309-10.

Cases involving the "purification" of a natural substance employ similar analysis. Our predecessor court recognized that merely purifying a naturally occurring substance does not render the substance patentable unless it results in a marked change in functionality. *In re Merz*, 97 F.2d 599, 601 (CCPA 1938) (holding that there was no right to a patent on a purer version of ultramarine, but recognizing that if a claimed article is "of such purity that it differs not only in degree but in kind it may be patentable"); *see also In re King*, 107 F.2d 618, 620 (CCPA 1939) (same, for purified vitamin C); *In re Marden*, 47 F.2d 958, 959 (CCPA 1931) (same, for purified vanadium);

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[4] By analogy, extracting a slab of marble from the earth does not give rise to protectable intellectual property rights, but "extracting" a piece of sculpture from that slab of marble does. In the case of the BRCA gene claims, what Myriad has claimed is more akin to the slab of marble found in the earth than to the sculpture carved from it after its extraction.

Gen. Elec. Co. v. DeForest Radio Co., 28 F.2d 641, 643 (3d Cir. 1928) (same, for purified tungsten). On the other hand, the purified natural substance is patentable if the "purification" results in a product with such distinct characteristics that it becomes "for every practical purpose a new thing commercially and therapeutically." *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95, 103 (C.C.S.D.N.Y. 1911); *see also Merck & Co. v. Olin Mathieson Chem. Corp.*, 253 F.2d 156, 161-64 (4th Cir. 1958) (holding that a purified composition of vitamin B-12 was patentable because the purification process resulted in a product that was therapeutically effective, whereas the natural form was not).

In sum, the test employed by the Supreme Court in *Chakrabarty* requires us to focus on two things: (1) the similarity in structure between what is claimed and what is found in nature and (2) the similarity in utility between what is claimed and what is found in nature. What is claimed in the BRCA genes is the genetic coding material; that material is the same, structurally and functionally, in both the native gene and the isolated form of the gene.

The structural differences between the claimed "isolated" genes and the corresponding portion of the native genes are irrelevant to the claim limitations, to the functioning of the genes, and to their utility in their isolated form. The use to which the genetic material can be put, i.e., determining its sequence in a clinical setting, is not a new use; it is only a consequence of possession. In order to sequence an isolated gene, each gene must function in the same manner in the laboratory as it does in the human body. Indeed, that identity of function in the isolated gene is the key to its value. The naturally occurring genetic material thus has not been altered in a way that would matter under the standard set forth in *Chakrabarty*. For that reason, the isolation of the naturally occurring genetic material does not make the claims to the isolated BRCA genes patent-eligible.

The Supreme Court's recent decision in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289, 1293 (2012), does not decide this case, but the Court's analysis is nonetheless instructive. In *Mayo*, which involved method claims, the representative claim involved the steps of administering a drug to a subject, determining a metabolite concentration in the subject's blood, and inferring the need for a change in dosage based on that metabolite concentration. *Id.* at 1295. The Court found that the method was not directed to patent-eligible subject matter because it contributed nothing "inventive" to the law of nature that lay at the heart of the claimed invention, i.e., "the relationships between the concentration in the blood of certain thiopurine metabolites and the likelihood that the drug dosage will be ineffective or induce harmful side-effects." *Id.* at 1294. The Court examined "whether the claims do significantly more than simply describe these natural relations" and whether the "claims add *enough* to their statements of the correlations to allow the processes they described to qualify as patent-eligible processes that apply natural laws." *Id.* at 1297 (emphasis in original). In concluding that the claims did not add "enough" to the natural laws, the Court was particularly persuaded by the fact that "the steps of the claimed processes . . . involve well-understood, routine, conventional activity previously engaged in by researchers in the field." *Id.* at 1294.

Just as a patent involving a law of nature must have an "inventive concept" that does "significantly more than simply describe . . . natural relations," *Mayo*, 132 S. Ct. at 1294, 1297, a patent involving a product of nature should have an inventive concept that involves more than merely incidental changes to the naturally occurring product. In cases such as this one, in which the applicant claims a composition of matter that is nearly identical to a product of nature, it is appropriate to ask whether the applicant has done "enough" to distinguish his alleged invention from the similar product of nature. Has the applicant made an "inventive" contribution to the product of nature? Does the claimed composition involve more than "well-understood, routine, conventional" elements? Here, the answer to those questions is no.

Neither isolation of the naturally occurring material nor the resulting breaking of covalent bonds makes the claimed molecules patentable. We have previously stated that "isolation of interesting compounds is a mainstay of the chemist's art," and that "[i]f it is known how to perform such an isolation doing so 'is likely the product not of innovation but of ordinary skill and common sense.'" *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1302 (Fed. Cir. 2007), quoting *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007). Similarly, the structural changes ancillary to the isolation of the gene do not render these claims patentable. The cleaving of covalent bonds incident to isolation is itself not inventive, and the fact that the cleaved molecules have terminal groups that differ from the naturally occurring nucleotide sequences does nothing to add any inventive character to the claimed molecules. The functional portion of the composition—the nucleotide sequence—remains identical to that of the naturally occurring gene.

The majority suggests that I have "focus[ed] not on the differences between isolated and native DNAs, but on one similarity: their informational content." In light of *Mayo*, that approach seems appropriate. The informational content of the nucleotide sequences is the critical aspect of these molecules; the terminal groups added to the molecules when the covalent bonds are broken—to which the majority and concurring opinions attribute such significance—are not even mentioned in the claims. The nucleotide sequences of the claimed molecules are the same as the nucleotide sequences found in naturally occurring human genes. In my view, that structural similarity dwarfs the significance of the structural differences between isolated DNA and naturally occurring DNA, especially where the structural differences are merely ancillary to the breaking of covalent bonds, a process that is itself not inventive.

II

As noted, in addition to the BRCA gene claims discussed above, the claims at issue in this appeal include four claims to BRCA cDNA and two claims to portions of the BRCA genes and cDNA as small as 15 nucleotides long.

I agree with the court that the claims to BRCA cDNA are eligible for patenting. The cDNA cannot be isolated from nature, but instead must be created in the laboratory.[5] The end product is a human-made invention with distinct structure because the introns that are found in the native gene are removed from the cDNA segment. Additionally, the cDNA has a utility not present in the naturally occurring BRCA DNA and mRNA because cDNA can be attached to a promoter and inserted into a non-human cell to drive protein expression.

However, I disagree with the court as to the two claims to short segments of DNA having at least 15 nucleotides. Claim 6 of the '282 patent covers any sequence of the BRCA1 cDNA that is at least 15 nucleotides long. That claim encompasses each BRCA1 exon, even though each exon is naturally defined by transcription. Moreover, because small sequences of DNA are repeated throughout the three billion nucleotides of the human genome, the claim covers portions of the cDNA of more than 4% of human genes. It also covers portions of the DNA of nearly all human genes. Accordingly, efforts to sequence almost any gene could infringe claim 6 even though Myriad's specification has contributed nothing to human understanding of other genes. Myriad is not entitled to such broad protection. *See Mayo*, 132 S. Ct. at 1301, 1303 (examining "how much future innovation is foreclosed relative to the contribution of the inventor" and warning of the "danger" that overly broad patent claims might

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[5] The appellees argue that the BRCA1 cDNA can be isolated from nature, and they refer to a BRCA1 pseudogene called BRCA1P1 that is found in the human genome. However, the appellees have failed to demonstrate that the pseudogene consists of the same sequence as the BRCA1 cDNA.

"foreclose[] more future invention than the underlying discovery could reasonably justify").

Myriad could easily have claimed more narrowly to achieve the utility it attaches to segments of cDNA. It contends that those segments can be used as probes and primers. DNA probes must be chemically altered or "tagged" before they can be so used, and Myriad could have claimed the tagged segments to achieve probe functionality. A claim to tagged segments would not encompass the BRCA1 exons. As to primer functionality, many of the cDNA segments will not work. Some will be too long. Some will be too short. Some will be palindromic and fold in on themselves. Myriad could have identified a subset of the segments that work as primers, and such a claim could be patentable if it were limited to species with "markedly different characteristics from any found in nature and . . . having the potential for significant utility." *Chakrabarty*, 447 U.S. at 310. The problem with claim 6 is that it is so broad that it includes products of nature (the BRCA1 exons) and portions of other genes; its validity is not salvaged because it includes some species that are not natural. Accordingly, I would hold claim 6 unpatentable.

The other claim to a short segment of DNA, claim 5 of the '282 patent, is breathtakingly broad. That claim covers any segment of the DNA defined by claim 1, provided that the segment is at least 15 nucleotides long. Claim 1, in turn, covers any isolated DNA that codes for the BRCA1 polypeptide. Thus, claim 5 would cover not only the isolated BRCA1 gene in each of its numerous molecular variations, but also any subsequence of those molecules, including portions that fall in the undefined range of those molecules denoted "vvvvvvvvvvvvvv." Claim 5 would therefore be unpatentable for the same reasons as claim 1 and claim 6.

Of course, in light of its breadth, claim 5 of the '282 patent is likely to be invalid on other grounds, and thus a ruling as to patent eligibility with respect to that claim may be superfluous. Nonetheless, it is important to consider the effects of such broad patent claims on the biotechnology industry. While Myriad has emphasized the biotechnology industry's need of patent protection to encourage and reward research in this difficult and important field, there is another side to the coin. Broad claims to genetic material present a significant obstacle to the next generation of innovation in genetic medicine—multiplex tests and whole-genome sequencing. New technologies are being developed to sequence many genes or even an entire human genome rapidly, but firms developing those technologies are encountering a thicket of patents. Secretary's Advisory Comm. on Genetics, Health, and Society, Dep't of Health & Human Servs., *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests* 49-62 (2010). In order to sequence an entire genome, a firm would have to license thousands of patents from many different licensors. *See id.* at 50-51. Even if many of those patents include claims that are invalid for anticipation or obviousness, the costs involved in determining the scope of all of those patents could be prohibitive. *See id.* at 51-52; Rebecca S. Eisenberg, *Noncompliance, Nonenforcement, Nonproblem? Rethinking the Anticommons in Biomedical Research*, 45 Hou. L. Rev. 1059, 1076-1080 (2008) (concluding that existing studies "have focused relatively little attention on downstream product development" and that interviews accompanying those studies suggest that, though smaller than initially feared, the costs associated with the patent thicket are "quite real in the calculations of product-developing firms").

My colleagues assign significant weight to the fact that since 2001 the PTO has had guidelines in place that have allowed patents on entire human genes. They conclude that those guidelines, and the PTO's earlier practice, are entitled to deference from this court as to the question whether patents to isolated human genes constitute patent-eligible subject matter. I think the PTO's practice and guidelines are not entitled to significant weight, for several reasons.

First, as we have recognized, the PTO lacks substantive rulemaking authority as to issues such as patentability. *Animal Legal Def. Fund v. Quigg*, 932 F.2d 920, 930 (Fed. Cir. 1991). In areas of patent scope, we owe deference only commensurate with "the thoroughness of its consideration and the validity of its reasoning." *Merck & Co. v. Kessler*, 80 F.3d 1543, 1550 (Fed. Cir. 1996). The comments that the PTO issued at the time of its 2001 guidelines in response to suggestions that isolated human genes were not patentable are, frankly, perfunctory. *See* John M. Conley & Roberte Makowski, *Back to the Future: Rethinking the Product of Nature Doctrine as a Barrier to Biotechnology Patents*, 85 J. Pat. & Trademark Off. Soc'y 301 (2003). Because those comments, at least on their face, do not reflect thorough consideration and study of the issue, I do not regard them as worthy of much weight in the analysis of this complex question.

Second, whatever force the PTO's views on the issue of patent eligibility may have had in the past has, at the very least, been substantially undermined by the position the government has taken in this case. The Department of Justice has twice filed a brief on behalf of the United States in this court taking the position that Myriad's gene claims (other than the cDNA claims) are not patent-eligible. Although the PTO did not "sign" the brief on either occasion and we are left to guess about the status of any possible continuing inter-agency disagreements about the issue, the Department of Justice speaks for the Executive Branch, and the PTO is part of the Executive Branch, so it is fair to conclude that the Executive Branch has modified its position from the one taken by the PTO in its 2001 guidelines and, informally, before that.

Finally, prior to the Supreme Court's decision in *Chakrabarty*, the PTO had determined that microorganisms were not subject to patenting, but the Supreme Court gave no indication that it regarded that view as entitled to deference. Moreover, the Court gave short shrift to the Commissioner's contention (which was made the lead argument in the government's brief in that case) that the patentability of life-forms was an issue that should be left to Congress. Citing *Marbury v. Madison*, 5 U.S. (1 Cranch) 137 (1803), the Court explained that "Congress has performed its constitutional role in defining patentable subject matter in § 101; we perform ours in construing the language Congress has employed." *Chakrabarty*, 477 U.S. at 315. We have the same responsibility and should not shy away from deciding the issues of law that the parties have brought to us. Although my colleagues believe our analysis of the legal question in this case should be influenced by purported expectations of the inventing community based on the PTO's past practice of issuing patents on human genes, that is in effect to give the PTO lawmaking authority that Congress has not accorded it.[6] There is no collective right of adverse possession to intellectual property, and we should not create one. Our role is to interpret the law that Congress has written in accordance with the governing precedents. I would do so and would affirm the district court's rulings as to the BRCA gene and BRCA gene segment claims.

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[6] Because the asserted reliance interest is based on PTO practice and not on prior judicial decisions, this case is not analogous to *Warner Jenkinson Co. v. Hilton Davis Chemical Co.*, 520 U.S. 17 (1997), or *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002), where the expectations of the inventing community were based on longstanding Supreme Court precedent.

United States Court of Appeals
for the Federal Circuit

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, THE AMERICAN COLLEGE OF MEDICAL GENETICS, THE AMERICAN SOCIETY FOR CLINICAL PATHOLOGY, THE COLLEGE OF AMERICAN PATHOLOGISTS, HAIG KAZAZIAN, MD, ARUPA GANGULY, PHD, WENDY CHUNG, MD, PHD, HARRY OSTRER, MD, DAVID LEDBETTER, PHD, STEPHEN WARREN, PHD, ELLEN MATLOFF, M.S., ELSA REICH, M.S., BREAST CANCER ACTION, BOSTON WOMEN'S HEALTH BOOK COLLECTIVE, LISBETH CERIANI, RUNI LIMARY, GENAE GIRARD, PATRICE FORTUNE, VICKY THOMASON, AND KATHLEEN RAKER,

No. 09-CV-4515

Plaintiffs-Appellees,

UNITED STATES PATENT AND TRADEMARK OFFICE,

Defendant,

MYRIAD GENETICS, INC.,

Defendant-Appellant,

LORRIS BETZ, ROGER BOYER, JACK BRITTAIN, ARNOLD B. COMBE, RAYMOND GESTELAND, JAMES U. JENSEN, JOHN KENDALL MORRIS, THOMAS PARKS, DAVID W. PERSHING, AND MICHAEL K. YOUNG, IN THEIR OFFICIAL CAPACITY AS DIRECTORS OF THE UNIVERSITY OF UTAH RESEARCH FOUNDATION,

Defendants-Appellants.

Appeal from the United States District Court for the Southern District of New York
Senior Judge Robert W. Sweet, Presiding.

Decided: July 29, 2011

Before LOURIE, BRYSON, and MOORE,

Circuit Judges.

Opinion for the court by *Circuit Judge* LOURIE.
Opinion concurring in part by *Circuit Judge* MOORE.

Opinion concurring in part and dissenting in part by *Circuit Judge* BRYSON.

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OPINION

LOURIE, *Circuit Judge*.

Myriad Genetics, Inc. and the Directors of the University of Utah Research Foundation (collectively, "Myriad") appeal from the decision of the United States District Court for the Southern District of New York holding that an assortment of medical organizations, researchers, genetic counselors, and patients (collectively, "Plaintiffs") have standing under the Declaratory Judgment Act to challenge Myriad's patents. *Assoc. for Molecular Pathology v. U.S. Patent & Trademark Office*, 669 F. Supp. 2d 365 (S.D.N.Y. 2009) ("*DJ Op.*"). Myriad also appeals from the district court's decision granting summary judgment that all of the challenged claims are drawn to non-patentable subject matter under 35 U.S.C. § 101. *Assoc. for Molecular Pathology v. U.S. Patent & Trademark Office*, 702 F. Supp. 2d 181 (S.D.N.Y. 2010) ("*SJ Op.*"). We affirm in part and reverse in part.

On the threshold issue of jurisdiction, we affirm the district court's decision to exercise declaratory judgment jurisdiction because we conclude that at least one plaintiff, Dr. Harry Ostrer, has standing to challenge the validity of Myriad's patents. On the merits, we reverse the district court's decision that Myriad's composition claims to "isolated" DNA molecules cover patent-ineligible products of nature under § 101 since the molecules as claimed do not exist in nature. We also reverse the district court's decision that Myriad's method claim to screening potential cancer therapeutics via changes in cell growth rates is directed to a patent-ineligible scientific principle. We, however, affirm the court's decision that Myriad's method claims directed to "comparing" or "analyzing" DNA sequences are patent ineligible; such claims include no transformative steps and cover only patent-ineligible abstract, mental steps.

BACKGROUND

Plaintiffs brought suit against Myriad, challenging the patentability of certain composition and method claims relating to human genetics. *See DJ Op.*, at 369-76. Specifically, Plaintiffs sought a declaration that fifteen claims from seven patents assigned to Myriad are drawn to patent-ineligible subject matter under 35 U.S.C. § 101: claims 1, 2, 5, 6, 7, and 20 of U.S. Patent 5,747,282 ("the '282 patent"); claims 1, 6, and 7 of U.S. Patent 5,837,492 ("the '492 patent"); claim 1 of U.S. Patent 5,693,473 ("the '473 patent"); claim 1 of U.S. Patent 5,709,999 ("the '999 patent"); claim 1 of U.S. Patent 5,710,001 ("the '001 patent"); claim 1 of U.S. Patent 5,753,441 ("the '441 patent"); and claims 1 and 2 of U.S. Patent 6,033,857 ("the '857 patent").

The challenged composition claims cover two "isolated" human genes, *BRCA1* and *BRCA2* (collectively, "*BRCA1/2*" or "*BRCA*"), and certain alterations, or mutations, in these genes associated with a predisposition to breast and ovarian cancers. Representative composition claims include claims 1, 2, and 5 of the '282 patent:

> 1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.

> 2. The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1.
>
> 5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.

SEQ ID NO:2 depicts the amino acid sequence of the BRCA1 protein, and SEQ ID NO: 1 depicts the nucleotide sequence of the *BRCA1* DNA coding region. '282 patent col.19 ll.48-50.

All but one of the challenged method claims cover methods of "analyzing" or "comparing" a patient's *BRCA* sequence with the normal, or wild-type, sequence to identify the presence of cancer-predisposing mutations. Representative method claims include claim 1 of the '999 and '001 patents:

> 1. A method for detecting a germline alteration in a BRCA1 gene, said alteration selected from the group consisting of the alterations set forth in Tables 12A, 14, 18 or 19 in a human which comprises *analyzing* a sequence of a BRCA1 gene or BRCA1 RNA from a human sample or *analyzing* a sequence of BRCA1 cDNA made from mRNA from said human sample with the proviso that said germline alteration is not a deletion of 4 nucleotides corresponding to base numbers 4184-4187 of SEQ ID NO:1.

'999 patent claim 1 (emphases added).

> 1. A method for screening a tumor sample from a human subject for a somatic alteration in a BRCA1 gene in said tumor which comprises [] *comparing* a first sequence selected from the group consisting of a BRCA1 gene from said tumor sample, BRCA1 RNA from said tumor sample and BRCA1 cDNA made from mRNA from said tumor sample with a second sequence selected from the group consisting of BRCA1 gene from a nontumor sample of said subject, BRCA1 RNA from said nontumor sample and BRCA1 cDNA made from mRNA from said nontumor sample, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said tumor sample from the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said nontumor sample indicates a somatic alteration in the BRCA1 gene in said tumor sample.

'001 patent claim 1 (emphasis added).

The final method claim challenged by Plaintiffs is directed to a method of screening potential cancer therapeutics. Specifically, claim 20 of the '282 patent reads as follows:

> 20. A method for screening potential cancer therapeutics which comprises: growing a transformed

> eukaryotic host cell containing an altered BRCA1 gene causing cancer in the presence of a compound suspected of being a cancer therapeutic, growing said transformed eukaryotic host cell in the absence of said compound, determining the rate of growth of said host cell in the presence of said compound and the rate of growth of said host cell in the absence of said compound and comparing the growth rate of said host cells, wherein a slower rate of growth of said host cell in the presence of said compound is indicative of a cancer therapeutic.

The challenged claims thus relate to isolated gene sequences and diagnostic methods of identifying mutations in these sequences. To place this suit in context, we take a step back to provide background on the science involved, including the identification of the *BRCA* genes, and the Plaintiffs' connections to the invention and to Myriad.

I.

Human genetics is the study of heredity in human beings.[1] The human genome, the entirety of human genetic information, contains approximately 25,000 genes, which form the basis of human inheritance. The majority of genes act by specifying polypeptide chains that form proteins. Proteins in turn make up living matter and catalyze all cellular processes.

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[1] The district court's opinion, *SJ Op.*, at 192-203, contains a detailed and comprehensive discussion of the science involved in this case. We repeat only the basics here.

Chemically, the human genome is composed of deoxyribonucleic acid ("DNA"). Each DNA molecule is made up of repeating units of four nucleotide bases—adenine ("A"), thymine ("T"), cytosine ("C"), and guanine ("G")—which are covalently linked, or bonded,[2] together via a sugar-phosphate, or phosphodiester, backbone. DNA generally exists as two DNA strands intertwined as a double helix in which each base on a strand pairs, or hybridizes, with a complementary base on the other strand: A pairs with T, and C with G. Figure 1 below depicts the structure of a DNA double helix and the complementary pairing of the four nucleotide bases, represented by A, T, C, and G.

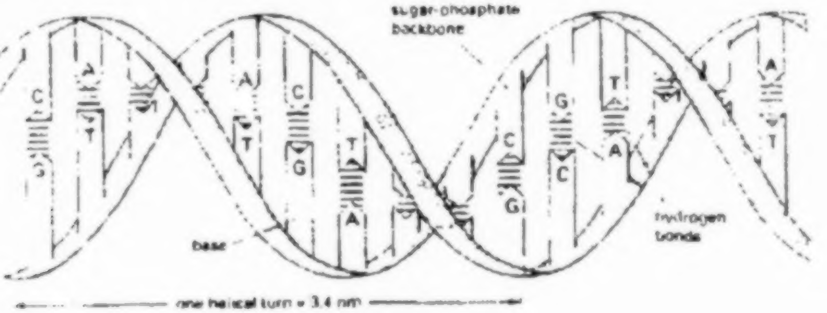

Figure 1

The linear order of nucleotide bases in a DNA molecule is referred to as its "sequence." The sequence of a gene is thus denoted by a linear sequence of As, Ts, Gs, and Cs. "DNA sequencing" or "gene sequencing" refers to the process by which the

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[2] Covalent bonds are chemical bonds characterized by the sharing of electrons between atoms in a molecule.

precise linear order of nucleotides in a DNA segment or gene is determined. A gene's nucleotide sequence in turn encodes for a linear sequence of amino acids that comprise the protein encoded by the gene, *e.g.*, the *BRCA1* gene encodes for the BRCA1 protein. Most genes have both "exon" and "intron" sequences. Exons are DNA segments that are necessary for the creation of a protein, *i.e.*, that code for a protein. Introns are segments of DNA interspersed between the exons that, unlike exons, do not code for a protein.

The creation of a protein from a gene comprises two steps: transcription and translation. First, the gene sequence is "transcribed" into a different nucleic acid called ribonucleic acid ("RNA"). RNA has a chemically different sugar-phosphate backbone than DNA, and it utilizes the nucleotide base uracil ("U") in place of thymine ("T"). For transcription, the DNA double helix is unwound and each nucleotide on the non-coding, or template, DNA strand is used to make a complementary RNA molecule of the coding DNA strand, *i.e.*, adenine on the template DNA strand results in uracil in the RNA molecule, thymine results in adenine, guanine in cytosine, and cytosine in guanine. The resulting "pre-RNA," like the DNA from which it was generated, contains both exon and intron sequences. Next, the introns are physically excised from the pre-RNA molecule, in a process called "splicing," to produce a messenger RNA ("mRNA"). Figure 2 below shows the steps of transcribing a gene that contains three exons (exon 1-3) and two introns (intron 1 and 2) into a pre-RNA, followed by RNA splicing of the introns to produce an mRNA containing just the exon sequences.

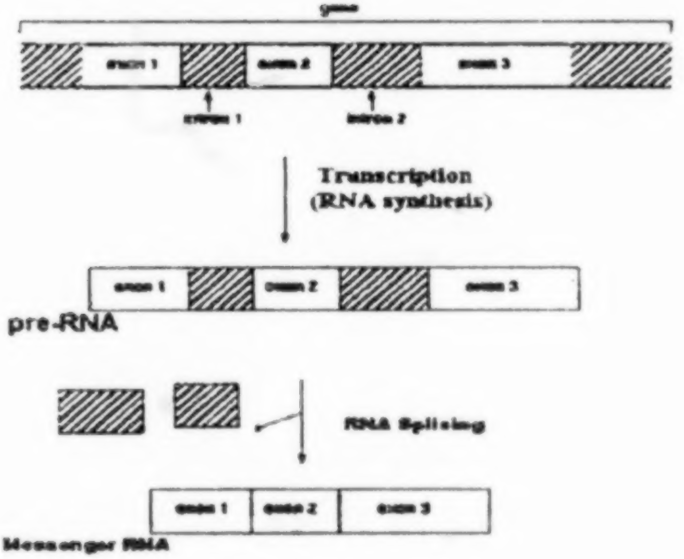
gene
exon 1
exon 2
exon 3
intron 1
intron 2
Transcription
(RNA synthesis)
exon 1
exon 2
exon 3
pre-RNA
RNA Splicing
exon 1
exon 2
exon 3
Messenger RNA

Figure 2

Following transcription, the resulting mRNA is "translated" into the encoded protein. Genes, and their corresponding mRNAs, encode proteins via three-nucleotide combinations called codons. Each codon corresponds to one of the twenty amino acids that make up all proteins or a "stop" signal that terminates protein translation. For example, the codon adenine-thymine-guanine (ATG, or UTG in the corresponding mRNA), encodes the amino acid methionine. The relationship between the sixty-four possible codon sequences and their corresponding amino acids is known as the genetic code. Figure 3 below represents an mRNA molecule that translates into a protein of six amino acids (Codon 1, AUG, methionine; Codon 2, ACG, threonine; Codon 3, GAG, glutamic acid; Codon 4, CUU, leucine; Codon 5, CGG, arginine; Codon 6, AGC, serine), and ends with one of the three stop codons, UAG.

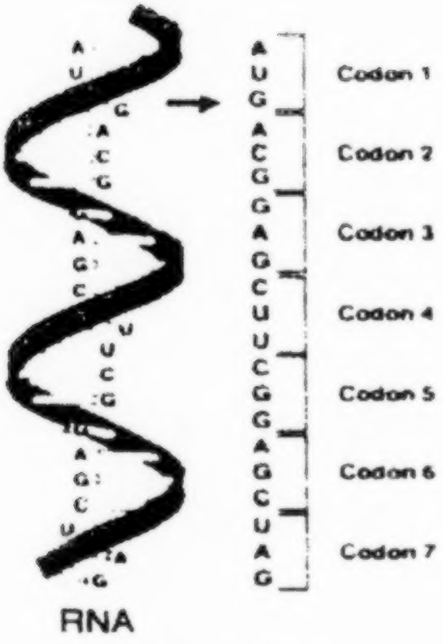

Figure 3

Changes, or mutations, in the sequence of a human gene can alter the structure as well as the function of the resulting protein. Small-scale changes include point mutations in which a change to a single nucleotide alters a single amino acid in the encoded protein. For example, a base change in the codon *G*CU to *C*GU changes an alanine in the encoded protein to an arginine. Larger scale variations include the deletion, rearrangement, or duplication of larger DNA segments, ranging from several hundreds to over a million nucleotides, and result in the elimination, misplacement, or duplication of an entire gene or genes. While some mutations have little or no effect on the body's processes, others result in disease, or an increased risk of developing a particular disease. DNA sequencing is used in clinical diagnostic testing to determine whether a gene contains mutations associated with a particular disease or risk of a particular disease.

Nearly every cell in the human body contains an individual's entire genome. DNA in the cell, called "native" or "genomic" DNA, is packaged into twenty-three pairs of chromosomes. Chromosomes are complex structures of a single DNA molecule wrapped around proteins called histones, as shown in Figure 4 below.

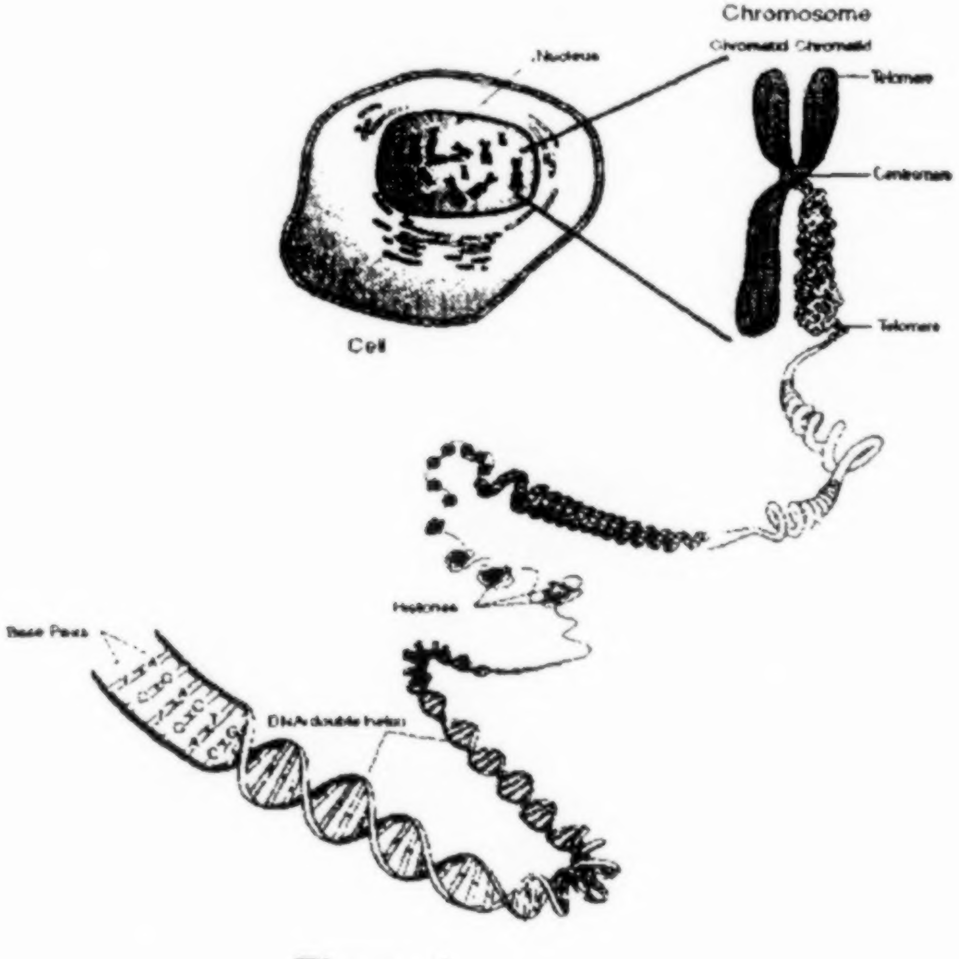
Chromosome
Chromatid Chromatid
Nucleus
Telomere
Centromere
Telomere
Cell
Histones
Base Pairs
DNA double helix

Figure 4

Humans have twenty-two pairs of autosomal chromosomes, numbered one to twenty-two according to size from largest to smallest, and one pair of sex chromosomes, two X chromosomes in females and one X and one Y chromosome in males.

Genomic DNA can be extracted from its cellular environment using a number of well-established laboratory techniques. A particular segment of DNA, such as a gene, can then be excised or amplified from the DNA to obtain the isolated DNA segment of interest. DNA molecules can also be synthesized in the laboratory. One type of synthetic DNA molecule is complementary DNA ("cDNA"). cDNA is synthesized from mRNA using complementary base pairing in a manner analogous to RNA transcription. The process results in a double-stranded DNA molecule with a sequence corresponding to the sequence of an mRNA produced by the body. Because it is synthesized from mRNA, cDNA contains only the exon sequences, and thus none of the intron sequences, from a native gene sequence.

II.

Mutations in the *BRCA* genes correlate with an increased risk of breast and ovarian cancer. The average woman in the United States has around a twelve to thirteen percent risk of developing breast cancer in her lifetime. Women with *BRCA* mutations, in contrast, face a cumulative risk of between fifty to eighty percent of developing breast cancer and a cumulative risk of ovarian cancer of between twenty to fifty percent. Diagnostic genetic testing for the existence of *BRCA* mutations is therefore an important consideration in the provision of clinical care for breast or ovarian cancer. This testing provides a patient with information on her risk for hereditary breast and ovarian cancers, and thus aids in the difficult decision regarding whether to undertake preventive options, including prophylactic surgery. Diagnostic results can also be an important factor in structuring an appropriate course of cancer treatment, since certain forms of chemotherapy are more effective in treating cancers related to *BRCA* mutations.

The inventors of the patents in suit identified the genetic basis of *BRCA1* and *BRCA2*-related cancers using an analysis called positional cloning. Relying on a large set of DNA samples from families with inherited breast and ovarian cancers, the inventors correlated the occurrence of cancer in individual family members with the inheritance of certain marker DNA sequences. This allowed the inventors to identify, or "map," the physical location of the *BRCA* genes within the human genome and to isolate the *BRCA* genes and determine their exact nucleotide sequences. This in turn allowed Myriad to provide *BRCA* diagnostic testing services to women.

Myriad filed the first patent application leading to the patents in suit covering isolated *BRCA1* DNA and associated diagnostic methods in August 1994. The first patent, the '473 patent, issued on December 2, 1997. Myriad filed the first application leading to the patents in suit covering isolated *BRCA2* DNA and associated diagnostic methods in December 1995, and the first patent, the '492 patent, issued on November 17, 1998.

III.

Myriad, however, was not the only entity to implement clinical *BRCA* testing services. Starting in 1996, the University of Pennsylvania's Genetic Diagnostic Laboratory ("GDL"), co-directed by plaintiffs Haig H. Kazazian, Jr., M.D. and Arupa Ganguly, Ph.D., provided *BRCA1/2* diagnostic services to women. By 1999, however, accusations by Myriad that GDL's *BRCA* testing services infringed its patents forced the lab to stop providing such services.

The first sign of a dispute came in early 1998. At that time, Dr. Kazazian recalls a dinner with Dr. Mark Skolnick, inventor and Chief Science Office at Myriad. At the dinner, Skolnick informed Kazazian that Myriad was planning to stop GDL from providing clinical *BRCA* testing in light of Myriad's patents. A month or two later, in May 1998, Kazazian received a letter from William A. Hockett, Director of Corporate Communications at Myriad. The letter stated that Myriad knew that Kazazian was currently providing *BRCA1* diagnostic testing services, and that Myriad, as patent holder of five patents covering the isolated *BRCA1* gene and diagnostic testing, was making available to select institutions a collaborative license. Attached to the letter was a copy of Myriad's collaborative agreement, which proposed severely limiting GDL's testing services to certain tests for patients of Ashkenazi Jewish descent. Plaintiff Harry Ostrer, M.D, a researcher at New York University ("NYU") School of Medicine, received the same letter and collaborative agreement in May 1998, although his laboratory did not, at the time, provide such testing services. Rather, Ostrer sent patient samples to GDL for *BRCA* genetic testing.

Months later, in August 1998, Dr. Kazazian received a second letter, this time from George A. Riley of the law firm O'Melveny & Myers LLP. The letter identified by number five Myriad patents "covering, among other things, the BRCA1 gene sequence . . . and methods for detecting alternations in the BRCA1 sequence." J.A. 1145. The letter also indicated that it "has come to Myriad's attention that you are engaged in commercial testing activities that infringe Myriad's patents," and that "[u]nless and until a licensing arrangement is completed . . . you should cease all infringing testing activity." *Id.* The letter noted, however, that the cease-and-desist notification did not apply to research testing "for the purpose of furthering non-commercial research programs, the results of which are not provided to the patient and for which no money is received from the patient or the patient's insurance." *Id.*

In June 1999, Robert Terrell, the General Counsel for University of Pennsylvania, received a similar cease-and-desist letter from Christopher Wight, Myriad's General Counsel. The letter stated, "It has come to our attention that Dr. Haig H. Kazazian, Jr. of the University of Pennsylvania is continuing to willfully engage in commercial BRCA1 and BRCA2 genetic testing activities, in violation of the University of Pennsylvania's previous assurances that such commercial testing activities would be discontinued." J.A. 2890. Terrell responded to Wight by letter on September 10, 1999, stating that "the University agrees that it will not accept samples for BRCA1 research testing from third parties." J.A.

2891. Kazazian thus informed Dr. Ostrer that GDL would no longer be accepting patient samples for *BRCA* testing from him or anyone else as a result of the patent infringement assertions made by Myriad. As a result, Ostrer started sending patient samples for *BRCA* genetic testing to Myriad, who became (and remains today) the only provider of such services in the United States.

During this period, Myriad also initiated several patent infringement suits against entities providing clinical *BRCA* testing. Myriad filed suit against Oncormed Inc. in 1997 and again in 1998, *Myriad Genetics v. Oncormed*, Nos. 2:97-cv-922, 2:98-cv-35 (D. Utah), and the University of Pennsylvania in 1998, *Myriad Genetics v. Univ. of Pa.*, No. 2:98-cv-829 (D. Utah). Both lawsuits were later dismissed without prejudice after each defendant agreed to discontinue all allegedly infringing activity.

None of the plaintiffs besides Drs. Kazazian, Ganguly, and Ostrer, allege that Myriad directed any letters or other communications regarding its patents at them. Rather, the other researchers and medical organization members state simply that knowledge of Myriad's vigorous enforcement of its patent rights against others stopped them from engaging in clinical *BRCA* genetic testing, although they have the personnel, expertise, and facilities as well as the desire to provide such testing. The patient plaintiffs state that they have been unable to obtain any *BRCA* genetic testing or their desired *BRCA* testing, either through their insurance or at a price that they can afford, because of Myriad's patent protection.

Like the other researchers, Dr. Kazazian states that if Myriad's patents were held invalid, he and Dr. Ganguly would be able to resume *BRCA* testing within a matter of a few weeks. He notes, however, that this is only if they "decided to resume BRCA testing." J.A. 2852. Ganguly concurs, stating that if the patents were invalidated, "I would immediately consider resuming BRCA testing in my laboratory." J.A. 2892. Ostrer also indicates that his lab has all the personnel, facilities, and expertise necessary to undertake clinical *BRCA* testing and emphatically states that his lab "would immediately begin to perform BRCA1/2-related genetic testing upon invalidation of the Myriad patents." J.A. 2936-38.

IV.

After Plaintiffs filed suit, Myriad moved to have the case dismissed, alleging that the Plaintiffs lacked standing to bring a declaratory judgment suit challenging the validity of its patents. The district court disagreed, however, holding that the Plaintiffs had established Article III standing under the "all the circumstances" test articulated by the Supreme Court in *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118, 127 (2007). *DJ Op.*, at 385-92. The court first found that Myriad had engaged in sufficient "affirmative acts" based on the company's assertion of its "right to preclude others from engaging in *BRCA1/2* genetic testing through personal communications, cease-and-desist letters, licensing offers, and litigation," the result of which was "the widespread understanding that one may engage in *BRCA1/2* testing at the risk of being sued for infringement liability by Myriad." *Id.* at 390. Myriad's actions, the court concluded, had placed "the Plaintiffs in precisely the situation that the

Declaratory Judgment Act was designed to address: the Plaintiffs have the ability and desire to engage in *BRCA1/2* testing as well as the belief that such testing is within their rights, but cannot do so without risking infringement liability." *Id.*

In so holding, the court rejected Myriad's argument that there must be some act directed toward the Plaintiffs, noting that Myriad had, in fact, taken affirmative acts toward plaintiffs Dr. Kazazian and Dr. Ganguly. *Id.* at 387-88. The court also rejected Myriad's arguments that the cease-and-desist letter sent to plaintiff Kazazian was too old to support declaratory judgment jurisdiction and that the legal actions brought against third parties could not be considered in the jurisdictional analysis. *Id.* at 388-89. The court concluded that rigid adherence to either of these requirements would be inconsistent with *MedImmune*'s mandate that the court assess the facts alleged under all the circumstances. *Id.*

The district court also found that the Plaintiffs had alleged sufficient meaningful preparations for infringement to establish declaratory judgment jurisdiction. *Id.* at 390-92. With respect to the researchers, the court held it was sufficient that they were all "ready, willing, and able" to begin *BRCA1/2* testing within the normal course of their laboratories' research, rejecting Myriad's argument that they needed to allege specific preparatory activities. *Id.* at 390-91. The court also rejected Myriad's argument that plaintiffs Kazazian and Ganguly testified only that they would "consider" engaging in allegedly infringing activities, concluding that the proper focus of the inquiry is whether they are meaningfully prepared, not whether they have made a final, conclusive decision to engage in such activities. *Id.* at 391 n.18.

The parties then moved for summary judgment on the merits of Plaintiffs' § 101 challenge to Myriad's patent claims. The district court held for Plaintiffs, concluding that the fifteen challenged claims were drawn to non-patentable subject matter and thus invalid under § 101. *SJ Op.*, at 220-37. Regarding the composition claims, the court held that isolated DNA molecules fall within the judicially created "products of nature" exception to § 101 because such isolated DNAs are not "markedly different" from native DNAs. *Id.* at 222, 232 (quoting *Diamond v. Chakrabarty*, 447 U.S. 303 (1980)). The court relied on the fact that, unlike other biological molecules, DNAs are the "physical embodiment of information," and that this information is not only preserved in the claimed isolated DNA molecules, but also essential to their utility as molecular tools. *Id.* at 228-32.

Turning to the method claims, the court held them patent ineligible under this court's then definitive machine-or-transformation test. *Id.* at 233 (citing *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008), *affirmed on other grounds by Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010)). The court held that the claims covered "analyzing" or "comparing" DNA sequences by any method, and thus covered mental processes independent of any physical transformations. *Id.* at 233-35. In so holding, the court distinguished Myriad's claims from those at issue in *Prometheus* based on the "determining" step in the latter being construed to include the extraction and measurement of metabolite levels from a patient sample. *SJ Op.*, at

234-35 (citing *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 628 F.3d 1347, 1350 (Fed. Cir. 2010), *cert. granted* 2011 WL 973139 (June 20, 2011)). Alternatively, the court continued, even if the claims could be read to include the transformations associated with isolating and sequencing human DNA, these transformations would constitute no more than preparatory data-gathering steps. *Id.* at 236 (citing *In re Grams*, 888 F.2d 835, 840 (Fed. Cir. 1989)). Finally, the court held that the one method claim to "comparing" the growth rate of cells claimed a basic scientific principle and that the transformative steps amounted to only preparatory data gathering. *Id.* at 237.

Myriad appealed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

I. Declaratory Judgment Jurisdiction

A.

The first question we must address is whether the district court correctly exercised declaratory judgment jurisdiction over this suit. The Declaratory Judgment Act provides that, "In a case of actual controversy within its jurisdiction . . . any court of the United States . . . may declare the rights and other legal relations of any interested party seeking such declaration, whether or not further relief is or could be sought." 28 U.S.C. § 2201(a). The phrase "a case of actual controversy" in the Act refers to the types of "cases" and "controversies" that are justiciable under Article III of the U.S. Constitution. *Aetna Life Ins. v. Haworth*, 300 U.S. 227, 239-40 (1937).

Although no bright-line rule exists for determining whether a declaratory judgment action satisfies Article III's case-or-controversy requirement, the Supreme Court has held that the dispute must be "definite and concrete, touching the legal relations of parties having adverse legal interests," "real and substantial," and "admi[t] of specific relief through a decree of a conclusive character, as distinguished from an opinion advising what the law would be upon a hypothetical state of facts." *MedImmune*, 549 U.S. at 127 (quoting *Aetna Life*, 300 U.S. at 240-41). "Basically, the question in each case is whether the facts alleged, under all the circumstances, show that there is a substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment." *Id.* (quoting *Md. Cas. Co. v. P. Coal & Oil Co.*, 312 U.S. 270, 273 (1941)).

In applying *MedImmune*'s all-the-circumstances test to a declaratory judgment action, we are guided by the Supreme Court's three-part framework for determining whether an action presents a justiciable Article III controversy: standing, ripeness, and mootness. *See Caraco Pharm. Labs., Ltd. v. Forest Labs., Inc.*, 527 F.3d 1278, 1291 (Fed. Cir. 2008). In this case, the parties have framed the jurisdictional issue as one of standing. *See MedImmune*, 549 U.S. at 128 n.8. ("The justiciability problem that arises, when the party seeking declaratory relief is himself preventing the complainedof injury from occurring, can be described in terms of standing . . . or . . . ripeness." (internal citations omitted)).

"[T]he irreducible constitutional minimum of standing contains three elements." *Lujan v. Defenders of Wildlife*, 504 U.S. 555, 560 (1992). "First, the plaintiff must have suffered an injury in fact—an invasion of a legally protected interest which is (a) concrete and particularized, and (b) actual or imminent, not conjectural or hypothetical." *Id.* (internal citations and quotations omitted). "Second, there must be a causal connection between the injury and the conduct complained of–the injury has to be 'fairly . . . trace[able] to the challenged action of the defendant . . . .'" *Id.* (quoting *Simon v. E. Ky. Welfare Rights Org.*, 426 U.S. 26, 41-42 (1976)). "Third, it must be 'likely,' as opposed to merely 'speculative,' that the injury will be 'redressed by a favorable decision.'" *Id.* at 561 (quoting *Simon*, 426 U.S. at 38, 43).

"Whether an actual case or controversy exists so that a district court may entertain an action for a declaratory judgment of non-infringement and/or invalidity is governed by Federal Circuit law." *MedImmune, Inc. v. Centocor, Inc.*, 409 F.3d 1376, 1378 (Fed. Cir. 2005), *overruled on other grounds*, *MedImmune*, 549 U.S. at 130-31. Following *MedImmune*, this court has held that, to establish an injury in fact traceable to the patentee, a declaratory judgment plaintiff must allege both (1) an affirmative act by the patentee related to the enforcement of his patent rights, *SanDisk Corp. v. STMicroelecs., Inc.*, 480 F.3d 1372, 1380-81 (Fed. Cir. 2007), and (2) meaningful preparation to conduct potentially infringing activity, *Cat Tech LLC v. TubeMaster, Inc.*, 528 F.3d 871, 880 (Fed. Cir. 2008). We review the exercise of declaratory judgment jurisdiction upon a particular set of facts *de novo*. *SanDisk Corp.*, 480 F.3d at 1377.

B.

Myriad challenges the district court's jurisdictional decision on the grounds that Myriad and the Plaintiffs do not have adverse legal interests and that Plaintiffs have failed to allege a controversy of sufficient immediacy and reality to warrant the issuance of a declaratory judgment. Specifically, Myriad argues that Plaintiffs have failed to allege any "affirmative acts" by Myriad within the past ten years relating to the patents in suit or directed at any Plaintiff. According to Myriad, the district court erred by relying on "stale communications" directed at Drs. Kazazian, Ganguly, and Ostrer over a decade ago, as well as ten-year-old licensing and litigation activities directed at third parties, and thus exercised jurisdiction based solely on Plaintiffs' subjective fear of suit, arising from rumor and innuendo in the research community.

Plaintiffs respond that they have standing under *MedImmune*'s all-the-circumstances test because, not only are they undisputedly prepared to immediately undertake potentially infringing activities, but also Myriad took sufficient affirmative acts with respect to the patents in suit. Regarding the latter, Plaintiffs assert that Myriad sued, threatened to sue, or demanded license agreements from every known institution offering *BRCA* clinical testing, including university labs directed by plaintiffs Kazazian, Ganguly, and Ostrer, forcing each to cease such testing. And, according to Plaintiffs, the awareness of Myriad's vigorous assertion of its patent rights still continues to suppress their ability to perform clinical *BRCA* testing, placing Plaintiffs in the very dilemma the Declaratory Judgment Act was intended to address: they must either proceed with *BRCA*-related activities and risk liability for patent infringement, or refrain from such activities despite believing Myriad's patents are invalid.

Under the facts alleged in this case, we conclude that one Plaintiff, Dr. Ostrer, has established standing to maintain this declaratory judgment suit. All Plaintiffs claim standing under the Declaratory Judgment Act based on the same alleged injury: that they cannot undertake the *BRCA*-related activities that they desire because of Myriad's enforcement of its patent rights covering *BRCA1/2*.[3] Only three plaintiffs, however, allege an injury traceable to Myriad; only Drs. Kazazian, Ganguly, and Ostrer allege affirmative patent enforcement actions directed at them by Myriad. Of these three, Dr. Ostrer clearly alleges a sufficiently real and imminent injury because he alleges an intention to actually and immediately engage in allegedly infringing *BRCA*-related activities. We address each in turn.

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[3] Certain patients also allege an injury based on their inability to gain access to affordable *BRCA* genetic testing because of Myriad's patent dominance of such services. While denial of health services can, in certain circumstances, state a judicially cognizable injury, *see Simon*, 426 U.S. at 40-41, Plaintiffs have not pressed this as an independent ground for standing. Moreover, we fail to see how the inability to afford a patented invention could establish an invasion of a legally protected interest for purposes of standing.

Although *MedImmune* relaxed this court's more restrictive "reasonable apprehension of suit" test for declaratory judgment jurisdiction, *SanDisk*, 480 F.3d at 1380, it did not alter "the bedrock rule that a case or controversy must be based on a *real* and *immediate* injury or threat of future injury that is *caused by the defendants*," *Prasco, LLC v. Medicis Pharm. Corp.*, 537 F.3d 1329, 1339 (Fed. Cir. 2008). Accordingly, following *MedImmune*, this court has continued to hold that declaratory judgment jurisdiction will not arise merely on the basis that a party learns of the existence of an adversely held patent, or even perceives that such a patent poses a risk of infringement, in the absence of some affirmative act by the patentee. *SanDisk*, 480 F.3d at 1380-81. Thus, without defining the outer boundaries of declaratory judgment jurisdiction, we have held that "where a patentee asserts rights under a patent based on certain identified ongoing or planned activity of another party, and where that party contends that it has the right to engage in the accused activity without license, an Article III case or controversy will arise . . . ." *Id.* at 1381; *see also Prasco*, 537 F.3d at 1338 ("A patentee can cause . . . an injury [sufficient to create an actual controversy] in a variety of ways, for example, by creating a reasonable apprehension of an infringement suit, [or] demanding the right to royalty payments." (internal citations omitted)).

In this case, Myriad demanded a royalty under its patents from Dr. Ostrer based on his clinical *BRCA*-related activities. In May 1998, Myriad's Director of Corporate Communications sent Ostrer a letter proposing a collaborative license. The letter stated that Myriad was aware that Ostrer was either currently providing, or was interested in initiating, *BRCA1* diagnostic testing services and that Myriad, as holder of U.S. patents covering the *BRCA1* gene and diagnostic testing of *BRCA1*, was making available to his institution, NYU Medical Center, a limited collaborative license. The collaborative license required NYU to make a payment to Myriad for each non-research *BRCA* test performed.

At the same time, as Ostrer was aware, Myriad was asserting its patent rights against other similarly situated parties, a fact to be considered in assessing the existence of an actual controversy under the totality of circumstances. *See Micron Tech., Inc. v. Mosaid Techs., Inc.*, 518 F.3d 897, 901 (Fed. Cir. 2008). Soon after Ostrer received Myriad's letter, Dr. Kazazian informed him that, because of Myriad's assertion of its patent rights against him, GDL would no longer be accepting patient samples for *BRCA* genetic testing. Myriad's assertion of its patent rights against Kazazian escalated into a patent infringement suit by Myriad against the University of Pennsylvania, which was later dismissed without prejudice after the University agreed to cease all accused *BRCA* testing services. Myriad also sued Oncormed for patent infringement based on its *BRCA* genetic testing services. As a result of Myriad's patent enforcement actions, Dr. Ostrer was forced to send all patient samples to Myriad, now the sole provider of *BRCA* diagnostic testing services.

Dr. Ostrer, on the other hand, maintains that he could have proceeded with his *BRCA*-related clinical activities without taking a license from Myriad. This assertion is based on his belief that the patents Myriad claims cover such activities are invalid because genes are patent-ineligible products of nature. Acting on his belief, Ostrer seeks in this lawsuit a declaration of his right to undertake *BRCA*-related clinical activities without a license. Accordingly, Myriad and Dr. Ostrer have taken adverse legal positions regarding whether or not Ostrer can engage in *BRCA* genetic testing without infringing any valid claim to "isolated" *BRCA* DNAs or methods of "analyzing" or "comparing" *BRCA* sequences, as recited in Myriad's patents. *See Aetna Life*, 300 U.S. at 242 (holding declaratory judgment jurisdiction existed when "the parties had taken adverse positions with respect to their existing obligations" on an insurance contract).

Dr. Ostrer has also alleged a controversy of sufficient reality and immediacy, *MedImmune*, 549 U.S. at 127; he has alleged a concrete and actual injury traceable to Myriad's assertion of its patent rights, *see Lujan*, 504 U.S. at 560. First, Ostrer seeks to undertake specific *BRCA*-related activities—*BRCA* diagnostic testing—for which Myriad has demanded a license under specific patents—those that cover the isolated *BRCA* genes and *BRCA* diagnostic testing. Thus, Ostrer does not request "an opinion advising what the law would be upon a hypothetical state of facts," *Aetna Life*, 300 U.S. at 241, but rather whether his proposed *BRCA* testing services are covered by valid patent claims to "isolated" *BRCA* genes and methods of "comparing" the genes' sequences. Second, Ostrer not only has the resources and expertise to immediately undertake clinical *BRCA* testing, but also states unequivocally that he will immediately begin such testing. In contrast to Ostrer, who alleges an actual and imminent injury for purposes of standing. Drs. Kazazian and Ganguly allege only that they will "consider" resuming *BRCA* testing. These "'some day' intentions" are insufficient to support an "actual or imminent" injury for standing "without . . . any specification of *when* the some day will be." *Lujan*, 504 U.S. at 564. As a result, Drs. Kazazian and Ganguly do not have standing.

Myriad seeks to escape this result based on the timing of its enforcement actions. Specifically, Myriad argues that time has extinguished the immediacy and reality of any controversy, relying on language that hearkens back to our pre-*MedImmune* reasonable apprehension of suit test. *See, e.g.*, Appellant Br. 26 ("[A] patentee's ten-year silence presumptively extinguishes any reasonable objective fear of suit."). We disagree. In many cases a controversy made manifest by a patentee's affirmative assertion of its patent rights will dissipate as market players and products change. In this case, however, the relevant circumstances surrounding Myriad's assertion of its patent rights have not changed despite the passage of time.[4]

Myriad's active enforcement of its patent rights forced Dr. Ostrer, as well as every other similarly situated researcher and institution, to cease performing the challenged *BRCA* testing services, leaving Myriad as the sole provider of *BRCA* clinical testing to patients in the United States. Since that time, neither the accused activities nor the parties' positions have changed. First, Myriad does not allege that genetic testing technology has changed in any way that renders its past assertions of its patent rights irrelevant to Ostrer's currently proposed *BRCA* testing. Rather, the patents cover, as Myriad asserted in the late 1990s, the basic components of any such test: the isolated *BRCA* genes and the diagnostic step of comparing the genes' sequences.

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[4] Myriad's analogy to laches is also unconvincing. Laches bars the recovery of pre-filing damages; it does not preclude a patent action for prospective relief, the type of relief sought here. *See A.C. Aukerman Co. v. R.L. Chaides Const. Co.*, 960 F.2d 1020, 1041 (Fed. Cir. 1992) (*en banc*) ("[L]aches bars relief on a patentee's claim only with respect to damages accrued prior to suit.").

Second, ever since Myriad's enforcement efforts eliminated all competition, Myriad and Ostrer have not altered their respective positions. Ostrer, still laboring under Myriad's threat of infringement liability, has not attempted to provide *BRCA* testing; yet, as a researcher, he remains in the same position with respect to his ability and his desire to provide *BRCA* testing as in the late 1990s. Furthermore, nothing in the record suggests that any researcher or institution has successfully attempted to compete with Myriad, or that Myriad has in any way changed its position with regard to its patent rights. Just as active enforcement of one's patent rights against others can maintain a real and immediate controversy despite the passage of time, *see Micron*, 518 F.3d at 901, so too can the successful assertion of such rights when the relevant circumstances remain unchanged. Thus, consistent with the purpose of the Declaratory Judgment Act, Ostrer need not risk liability and treble damages for patent infringement before seeking a declaration of his contested legal rights. *See MedImmune*, 549 U.S. at 134.

Myriad also argues that the record refutes Ostrer's claim that he has been restrained from engaging in *BRCA*-related gene sequencing. Specifically, Myriad argues that since Myriad published its discoveries of the *BRCA1* and *BRCA2* genes in October 1994 and March 1996, respectively, over 18,000 scientists have conducted research on the *BRCA* genes and over 8,600 research papers have been published. Furthermore, according to Myriad, plaintiff Wendy Chung concedes that her lab currently conducts sequencing of *BRCA* genes. Yet, both Drs. Chung and Ostrer state that, although they conduct gene sequencing, they are forbidden from informing their research subjects of the results of their *BRCA* tests without first sending the samples to Myriad. Accordingly, Ostrer is restrained from the *BRCA*-related activity that he desires to undertake: clinical diagnostic testing.

Myriad's communications with Dr. Ostrer confirm this understanding. The licensing letter Myriad sent to Ostrer proposed a collaborative agreement giving NYU the right to perform "Research Tests" without payment to Myriad. J.A. 2967. "Research Tests" are defined as tests that further "non-commercial research programs, the results of which *are not provided to the patient* and for which no money is received." J.A. 2965 (emphasis added). In contrast, the agreement requires payment to Myriad for each "Testing Service" performed, with "Testing Services" defined as "medical laboratory testing . . . for the presence or absence of BRCA1 mutations for the purpose of determining or predicting predisposition to, or assessing the risk of breast or ovarian cancer in humans." J.A. 2966-67. Thus, Myriad's patent enforcement actions never targeted the non-clinical *BRCA* research now cited by Myriad, and Ostrer's ability to perform such research does not address the injury asserted here.

Finally, Myriad argued in its reply brief and at oral argument that Plaintiffs' declaratory action will not afford them the relief they want, a requirement for standing. *Lujan*, 504 U.S. at 560-61; *see also MedImmune*, 549 U.S. at 127 n.7 ("[A] litigant may not use a declaratory-judgment action to obtain piecemeal adjudication of defenses that *would not finally and conclusively resolve* the underlying controversy."). Specifically, Myriad asserts that because Plaintiffs have challenged just fifteen composition and method claims, while admitting that other unchallenged claims to *BRCA* probes and primers will still prevent them from engaging in *BRCA* sequencing, a favorable decision will not redress the Plaintiffs' alleged injury. Again, we disagree.

The Supreme Court has required only that it is "likely," rather than "merely 'speculative,'" that the alleged injury will be "redressed by a favorable decision." *Lujan*, 504 U.S. at 561. The Court has not required certainty. For example, in *Village of Arlington Heights v. Metropolitan Housing Development Corp.*, the Court held that the plaintiffs had standing to challenge a suburb's exclusionary zoning ordinance, as the ordinance stood as "an absolute barrier" to the housing development Metropolitan Housing Development Corp. ("MHDC") had contracted to provide in the village. 429 U.S. 252, 261 (1977). The Court noted that injunctive relief, while removing the "barrier" of the ordinance, would not "guarantee" that the housing would be built since MHDC still had to secure financing, qualify for federal subsidies, and carry through with construction. *Id.* The Court nevertheless recognized that "all housing developments are subject to some extent to similar uncertainties," and concluded that it was sufficient that there was a "substantial probability" that the housing development would be built. *Id.* at 261, 264.

In this case, Myriad's challenged composition and method claims undisputedly provide "an absolute barrier" to Dr. Ostrer's ability to undertake *BRCA* diagnostic testing activities, and a declaration of those claims' invalidity would remove that barrier. *See id.* at 261. Moreover, while there may be other patent claims directed to *BRCA* probes and primers that prevent Ostrer from performing *BRCA* diagnostic testing free of infringement liability, Myriad has failed to direct us to any specific unchallenged claim that will have that effect. And Plaintiffs' counsel stated at oral argument that his clients can sequence the *BRCA* genes without using *BRCA* probes and primers. Oral Arg. at 34:07-25, 34:53-35:29 *available at* http://www.cafc.uscourts.gov/oral-argument-recordings/2010-1406/all. Accordingly, we decline to construe claims and hold on this record that Dr. Ostrer's proposed *BRCA*-related activities would infringe unchallenged claims to primers and probes. We thus conclude that it is likely, not merely speculative, that Dr. Ostrer's injury will be redressed by a favorable decision.

Accordingly, although we affirm the district court's decision to exercise declaratory judgment jurisdiction, we affirm on much narrower grounds. The district court failed to limit its jurisdictional holding to affirmative acts by the patentee directed at specific Plaintiffs, *see SanDisk*, 480 F.3d at 1380-81, erroneously holding all the Plaintiffs had standing based on "the widespread understanding that one may engage in *BRCA1/2* testing at the risk of being sued for infringement liability by Myriad," *DJ Op.*, at 390. We disagree, and thus we reverse the district court's holding that the various plaintiffs other than Dr. Ostrer have standing to maintain this declaratory judgment action. Simply disagreeing with the existence of a patent or even suffering an attenuated, non-proximate, effect from the existence of a patent does not meet the Supreme Court's requirement for an adverse legal controversy of sufficient immediacy and reality to warrant the issuance of a declaratory judgment. *See MedImmune*, 549 U.S. at 127.

Having found one plaintiff with standing to maintain this declaratory judgment action, *see Horne v. Flores*, 129 S. Ct. 2579, 2592-93 (2009), we may turn now to the merits of Myriad's appeal of the district court's summary judgment decision, which held all fifteen challenged composition and method claims invalid under § 101.

II. Patentable Subject Matter

Under the Patent Act, "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101. The Supreme Court has consistently construed § 101 broadly, explaining that "[i]n choosing such expansive terms . . . modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope." *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010) (quoting *Chakrabarty*, 447 U.S. at 308).

The Supreme Court, however, has also consistently held that § 101, although broad, is not unlimited. *Id.* The Court's precedents provide three judicially created exceptions to § 101's broad patent-eligibility principles: "laws of nature, physical phenomena, and abstract ideas." *Id.* (quoting *Chakrabarty*, 447 U.S. at 309). The Court has also referred to these exceptions as precluding the patenting of phenomena of nature, mental processes, *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972), and products of nature, *Chakrabarty*, 447 U.S. at 313 ("[T]he relevant distinction for purposes of § 101 is ...between products of nature . . . and human-made inventions."). The Court has explained that, although not required by the statutory text, "[t]he concepts covered by these exceptions are 'part of the storehouse of knowledge of all men . . . free to all men and reserved exclusively to none.'" *Bilski*, 130 S. Ct. at 3225 (quoting *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948))

Plaintiffs challenge under § 101 Myriad's composition claims directed to "isolated" DNA molecules and method claims directed to "analyzing" or "comparing" DNA sequences. We address each in turn.

A. Composition Claims: Isolated DNA Molecules

i.

Myriad argues that its challenged composition claims to "isolated" DNAs cover patent-eligible compositions of matter within the meaning of § 101. According to Myriad, the district court came to a contrary conclusion by (1) misreading Supreme Court precedent as excluding from patent eligibility all "products of nature" unless "markedly different" from naturally occurring ones; and (2) incorrectly focusing not on the differences between isolated and native DNAs, but on one similarity: their informational content. Rather, Myriad argues, an isolated DNA molecule is patent eligible because it is, as claimed, "a nonnaturally occurring composition of matter" with "a distinctive name, character, and use." Appellant Br. 41-42 (quoting *Chakrabarty*, 447 U.S. at 309-10). According to Myriad, isolated DNA does not exist in nature, and isolated DNAs, unlike native DNAs, can be used as primers and probes for diagnosing cancer. Moreover, Myriad asserts that a categorical "products of nature" exception not only would be unworkable, as every composition of matter is, at some level, composed of natural materials, but also would be contrary to this court's precedents, the PTO's 2001 *Utility Examination Guidelines*, and Congress's role in enacting the patent laws.

Plaintiffs respond that claims to isolated DNA molecules fail to satisfy § 101 because such claims cover natural phenomena and products of nature. According to Plaintiffs, Supreme Court precedent establishes that a product of nature is not patent eligible even if, as claimed, it has undergone some highly useful change from its natural form. Rather, Plaintiffs assert, to be patent eligible a composition of matter must also have a distinctive name, character, and use, making it "markedly different" from the natural product. In this case, Plaintiffs conclude that because isolated DNAs retain the same nucleotide sequence as native DNAs, they do not have any "markedly different" characteristics. Furthermore, according to Plaintiffs, the isolated DNA claims also have a preemptive effect, excluding anyone from working with the *BRCA* genes.

The government as amicus curiae does not defend the PTO's longstanding position that isolated DNA molecules are patent eligible, arguing instead for a middle ground. Specifically, the government argues that DNA molecules engineered by man, including cDNAs,[5] are patent-eligible compositions of matter because, with rare exceptions, they do not occur in nature, either in isolation or as contiguous sequences within a chromosome. In contrast, the government asserts, isolated and unmodified genomic DNAs are *not* patent eligible, but rather patent-ineligible products of nature, since their nucleotide sequences exist because of evolution, not man.

At oral argument, the government illustrated its argument by way of a "magic microscope" test. Oral Arg. at 46:50-47:50. According to the government's test, if an imaginary microscope could focus in on the claimed DNA molecule as it exists in the human body, the claim covers unpatentable subject matter. The government thus argues that because such a microscope could focus in on the claimed isolated *BRCA1* or *BRCA2* sequences as they exist in the human body, the claims covering those sequences are not patent eligible. In contrast, the government contends, because an imaginary microscope could not focus *in vivo* on a cDNA sequence, which is engineered by man to splice together non-contiguous coding sequences (*i.e.*, exons), claims covering cDNAs are patent eligible.

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[5] According to the government, several of the composition claims at issue in this suit, including claim 2 of the '282 patent, are limited to cDNA and thus patent eligible.

In sum, although the parties and the government appear to agree that isolated DNAs are compositions of matter, they disagree on whether and to what degree such molecules fall within the exception for products of nature. As set forth below, we conclude that the challenged claims to isolated DNAs, whether limited to cDNAs or not, are directed to patent-eligible subject matter under § 101.

ii.

The Supreme Court's decisions in *Chakrabarty* and *Funk Brothers* set out the framework for deciding the patent eligibility of isolated DNA molecules.[6]

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[6] Other Supreme Court decisions cited by the parties and amici were decided based on lack of novelty, not patentable subject matter. In *American Wood-Paper Co. v. Fibre Disintegrating Co.*, the Court held the challenged patent "void for want of novelty in the manufacture patented," because the "[p]aper-pulp obtained from various vegetable substances was in common use before the original patent was granted . . . , and whatever may be said of their process for obtaining it, the product was in no sense new." 90 U.S. 566, 596 (1874). Similarly, in *Cochrane v. Badische Anilin & Soda Fabrik*, the Court held that a claim to artificial alizarine covered an old and well-known substance, the alizarine of madder, which could not be patented although made artificially for the first time. 111 U.S. 293, 311 (1884); *see also id.* at 308-09 ("It is very plain that the specification of the original patent, No. 95,465, states the invention to be a process for preparing alizarine, *not as a new substance prepared for the first time*, but as the substance already known as alizarine, to

In *Chakrabarty*, the Court addressed the question whether a man-made, living microorganism is a patentable manufacture or composition of matter within the meaning of § 101. 447 U.S. at 305, 307. The microorganisms were bacteria genetically engineered with four naturally occurring DNA plasmids, each of which enabled the breakdown of a different component of crude oil. *Id.* at 305, 305 n.1. The bacteria, as a result, could break down multiple components of crude oil, a trait possessed by no single naturally occurring bacterium and of significant use in more efficiently treating oil spills. *Id.* at 305, 305 n.2. The Court held that the bacteria qualified as patentable subject matter because the "claim is not to a hitherto unknown natural phenomenon, but to a non-naturally occurring manufacture or composition of matter—a product of human ingenuity 'having a distinctive name, character [and] use.'" *Id.* at 309-10 (quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887)).

To underscore the point, the Court compared Chakrabarty's engineered bacteria with bacteria inoculants found unpatentable in *Funk Brothers*, again casting this case decided on obviousness in terms of § 101. *See Parker v. Flook*, 437 U.S. 584, 591 (1978); *Benson*, 409 U.S. at 67. In *Funk Brothers*, the patentee discovered that certain strains of nitrogen-fixing bacteria associated with leguminous plants do not mutually inhibit each other. 333 U.S. at 129-30. Based on this discovery, the patentee produced (and claimed) mixed cultures of nitrogen-fixing species

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be prepared, however, by the new process, which process is to be the subject of the patent, and is the process of preparing the *known product* alizarine from anthracine." (emphases added)).

capable of inoculating a broader range of leguminous plants than single-species cultures. *Id.* The Court held that the bacteria's qualities of non-inhibition were, "like the heat of the sun, electricity, or the qualities of metals," the "work of nature," and thus not patentable. *Id.* at 130. The Court also held that application of the newly discovered bacterial trait of non-inhibition to create a mixed bacterial culture was not a patentable advance because no species acquired a different property or use. *Id.* at 131. The *Chakrabarty* Court thus concluded that what distinguished Chakrabarty's bacteria from those claimed in *Funk Brothers*, and made the former patent eligible, was that Chakrabarty's bacteria had "markedly different characteristics from any [bacterium] found in nature" based on the efforts of the patentee. *Chakrabarty*, 447 U.S. at 310.

The distinction, therefore, between a product of nature and a human-made invention for purposes of § 101 turns on a change in the claimed composition's identity compared with what exists in nature. Specifically, the Supreme Court has drawn a line between compositions that, even if combined or altered in a manner not found in nature, have similar characteristics as in nature, and compositions that human intervention has given "markedly different," or "distinctive," characteristics. *Id.* *Hartranft*, 121 U.S. at 615; *see also Am. Fruit Growers v. Brogdex Co.*, 283 U.S. 1, 11 (1931). Applying this test to the isolated DNAs in this case, we conclude that the challenged claims are drawn to patentable subject matter because the claims cover molecules that are markedly different—have a distinctive chemical identity and nature—from molecules that exist in nature.

It is undisputed that Myriad's claimed isolated DNAs exist in a distinctive chemical form—as distinctive chemical molecules—from DNAs in the human body, *i.e.*, native DNA. Native DNA exists in the body as one of forty-six large, contiguous DNA molecules. Each DNA molecule is itself an integral part of a larger structural complex, a chromosome. In each chromosome, the DNA molecule is packaged around histone proteins into a structure called chromatin, which in turn is packaged into the chromosomal structure. *See supra*, Figure 3.

Isolated DNA, in contrast, is a free-standing portion of a native DNA molecule, frequently a single gene. Isolated DNA has been cleaved (*i.e.*, had covalent bonds in its backbone chemically severed) or synthesized to consist of just a fraction of a naturally occurring DNA molecule. For example, the *BRCA1* gene in its native state resides on chromosome 17, a DNA molecule of around eighty million nucleotides. Similarly, *BRCA2* in its native state is located on chromosome 13, a DNA of approximately 114 million nucleotides. In contrast, isolated *BRCA1* and *BRCA2*, with introns, each consists of just 80,000 or so nucleotides. And without introns, *BRCA2* shrinks to just 10,200 or so nucleotides and *BRCA1* to just around 5,500 nucleotides. Furthermore, claims 5 and 6 of the '282 patent cover isolated DNAs having as few as fifteen nucleotides of a *BRCA* sequence. Accordingly, *BRCA1* and *BRCA2* in their isolated state are not the same molecules as DNA as it exists in the body; human intervention in cleaving or synthesizing a portion of a native chromosomal DNA imparts on that isolated DNA a distinctive chemical identity from that possessed by native DNA.

As the above description indicates, isolated DNA is not purified DNA. Purification makes pure what was the same material, but was previously impure. Although isolated DNA must be removed from its native cellular and chromosomal environment, it has also been manipulated chemically so as to produce a molecule that is markedly different from that which exists in the body. It has not been purified by being isolated. Accordingly, this is not a situation, as in *Parke-Davis & Co. v. H.K. Mulford Co.*, in which purification of adrenaline resulted in the *identical* molecule being "for every practical purpose a new thing commercially and therapeutically." 189 F. 95, 103 (C.C.N.Y. 1911). Although, we note, Judge Learned Hand held the claimed purified "Adrenalin" to be patentable subject matter. *Id.* The *In re Marden* cases are similarly inapposite,[7] directed as they are to the patent ineligibility of purified natural elements—ductile uranium, 47 F.2d 957 (CCPA 1931), and vanadium, 47 F.2d 958 (CCPA 1931)—that are inherently ductile in purified form. *Parke-Davis* and *Marden* address a situation in which claimed compound A is purified from a physical mixture that contains compound A. In this case, the claimed isolated DNA molecules do not exist as in nature within a physical mixture to be purified. They have to be chemically cleaved from their chemical combination with other genetic materials. In other words, in nature, isolated DNAs are covalently bonded to such other materials. Thus, when cleaved, an isolated DNA molecule is not a purified form of a natural material, but a distinct chemical entity. In fact, some forms of isolated DNA require no purification at all, because DNAs can be chemically synthesized directly as isolated molecules.

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[7] We note that *Bergy* is no longer binding law. *Bergy* was the companion case to *Charkarbarty*, and was vacated by the Supreme Court and remanded for dismissal as moot. *Diamond v. Chakrabarty*, 444 U.S. 1028 (1980). Other CCPA cases cited by the parties and amici were not decided based on patent eligibility. In *In re Bergstrom*, the court held that pure prostaglandin compounds, PGE(2) and PGE(3), were improperly rejected as lacking novelty. 427 F.2d 1394, 1394 (CCPA 1970); *see Bergy*, 596 F.2d at 961 (recognizing *Bergstrom* as a case decided under § 102). Similarly in *In re Kratz*, the court held non-obviousness claims to synthetically produced, substantially pure 2-methyl-2-pentenoic acid ("2M2PA"), a chemical that gives strawberries their flavor. 592 F.2d 1169, 1170 (CCPA 1979); *see also In re King*, 107 F.2d 618, 619 (CCPA 1939) (holding claims to vitamin C invalid for lack of novelty, as "[a]ppellants were not the first to discover or produce [vitamin C] in its pure form"); *In re Merz*, 97 F.2d 599, 601 (CCPA 1938) (holding claims to artificial ultramarine that contains non-

The dissent disparages the significance of a "chemical bond," presumably meaning a covalent bond, in distinguishing structurally between one molecular species and another. But a covalent bond is the defining boundary between one molecule and another. The dissent's citation of Linus Pauling's comment that covalent bonds "make it convenient for the chemist to consider [the aggregate] as an independent molecular species" underlines the point. The covalent bonds in this case separate one chemical species from another.

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floatable impurities invalid as not "inventive," and thus as obvious).

Plaintiffs argue that because the claimed isolated DNAs retain the same nucleotide sequence as native DNAs, they do not have any "markedly different" characteristics. This approach, however, looks not at whether isolated DNAs are markedly different—have a distinctive characteristic—from naturally occurring DNAs, as the Supreme Court has directed, but at one similarity: the information content contained in isolated and native DNAs' nucleotide sequence. Adopting this approach, the district court disparaged the patent eligibility of isolated DNA molecules because their genetic function is to transmit information. We disagree, as it is the distinctive nature of DNA molecules as isolated compositions of matter that determines their patent eligibility rather than their physiological use or benefit. Uses of chemical substances may be relevant to the non-obviousness of these substances or to method claims embodying those uses, but the patent eligibility of an isolated DNA is not negated because it has similar informational properties to a different, more complex natural material that embodies it. The claimed isolated DNA molecules are distinct from their natural existence as portions of larger entities, and their informational content is irrelevant to that fact. We recognize that biologists may think of molecules in terms of their uses, but genes are in fact materials having a chemical nature and, as such, are best described in patents by their structures rather than their functions.

The district court in effect created a categorical rule excluding isolated genes from patent eligibility. *See SJ Op.*, at 228-29. But the Supreme Court has "more than once cautioned that courts 'should not read into the patent laws limitations and conditions which the legislature has not expressed,'" *Bilski*, 130 S. Ct. at 3226 (quoting *Diamond v. Diehr*, 450 U.S. 175, 182 (1981)), and has repeatedly rejected new categorical exclusions from § 101's scope, *see id.* at 3227-28 (rejecting the argument that business method patents should be categorically excluded from § 101); *Chakrabarty*, 447 U.S. at 314-17 (same for living organisms). We therefore reject the district court's unwarranted categorical exclusion of isolated DNA molecules.

Because isolated DNAs, not just cDNAs, have a markedly different chemical structure compared to native DNAs, we reject the government's proposed "magic microscope" test, as it misunderstands the difference between science and invention and fails to take into account the existence of molecules as separate chemical entities. The ability to visualize a DNA molecule through a microscope, or by any other means, when it is bonded to other genetic material, is worlds apart from possessing an isolated DNA molecule that is in hand and usable. It is the difference between knowledge of nature and reducing a portion of nature to concrete form, the latter activity being what the patent laws seek to encourage and protect. The government's microscope could focus in on a claimed portion of any complex molecule, rendering that claimed portion patent ineligible, even though that portion never exists as a separate molecule in the body or anywhere else in nature, and may have an entirely different utility. That would discourage innovation. One cannot visualize a portion of a complex molecule, including a DNA containing a particular gene, and will it into isolation as a unique entity. Visualization does not cleave and isolate the particular DNA; that is the act of human invention.

The parties and amici have provided many thought-provoking hypotheticals, each of which raises a complicated issue of patent eligibility not before the court. Accordingly, we address them only briefly; courts decide cases, they do not draft legal treatises. It is suggested that holding isolated DNAs patent eligible opens the door to claims covering isolated chemical elements, like lithium; minerals found in the earth, like diamonds; atomic particles, like electrons; and even organs, like a kidney, and a leaf from a tree. None of these examples, however, as far as we can discern, presents the case of a claim to a composition having a distinctive chemical identity from that of the native element, molecule, or structure. Elemental lithium is the same element whether it is in the earth or isolated; the diamond is the same lattice of carbon molecules, just with the earth removed; the kidney is the same kidney, the leaf the same leaf. Some may have a changed form, quality, or use when prepared in isolated or purified form, but we cannot tell on this record whether the changes are sufficiently distinctive to make the composition markedly different from the one that exists in nature. In contrast, a portion of a native DNA molecule—an isolated DNA—has a markedly different chemical nature from the native DNA. It is, therefore, patentable subject matter.

The dissent indicates that we "acknowledge[] that elemental lithium (like other elements) would not be patentable subject matter because it 'is the same element whether it is in earth or isolated.'" Again, these facts are not before us, so we do not attempt to evaluate the patentability of one form of lithium over another. Suffice it to say, however, that if lithium is found in the earth as other than elemental lithium, such as "in molecular form" "because it reacts with air and water," it is not the same material as elemental lithium.

It is also important to dispute the dissent's analogy to snapping a leaf from a tree. With respect, no one could contemplate that snapping a leaf from a tree would be worthy of a patent, whereas isolating genes to provide useful diagnostic tools and medicines is surely what the patent laws are intended to encourage and protect. Snapping a leaf from a tree is a physical separation, not one creating a new chemical entity.

The dissent also mentions several times in its opinion the breadth of certain claims as grounds for objecting to their patentability. However, we do not have here any rejection or invalidation on the various grounds relating to breadth, such as in 35 U.S.C. § 112. The issue before us is patent eligibility, not the adequacy of the patents' disclosure to support particular claims.

Finally, our decision that isolated DNA molecules are patent eligible comports with the longstanding practice of the PTO. The Supreme Court has repeatedly stated that changes to longstanding practice should come from Congress, not the courts. In *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred International, Inc.*, the Court rejected the argument that plants did not fall within the scope of § 101, relying in part on the fact that "the PTO has assigned utility patents for plants for at least 16 years and there has been no indication from either

Congress or agencies with expertise that such coverage is inconsistent with [federal law]." 534 U.S. 124, 144-45 (2001); *see also Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002) ("[C]ourts must be cautious before adopting changes that disrupt the settled expectations of the inventing community." (citing *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 28 (1997))); *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1347 (Fed. Cir. 2010) (upholding a written description requirement separate from enablement based in part on *stare decisis*).

In this case, the PTO has issued patents directed to DNA molecules for almost thirty years. In the early 1980s, the Office granted the first human gene patents. *See* Eric J. Rogers, *Can You Patent Genes? Yes and No*, 93 J. Pat. & Trademark Off. Soc'y 19 (2010). It is estimated that the PTO has issued 2,645 patents claiming "isolated DNA" over the past twenty-nine years, J.A. 3710, and that by 2005, had granted 40,000 DNA-related patents covering, in non-native form, twenty percent of the genes in the human genome, Rogers, *supra* at 40. In 2001, the PTO issued *Utility Examination Guidelines*, which reaffirmed the agency's position that isolated DNA molecules are patent eligible, 66 Fed. Reg. 1092-94 (Jan. 5, 2001), and Congress has not indicated that the PTO's position is inconsistent with § 101. If the law is to be changed, and DNA inventions excluded from the broad scope of § 101 contrary to the settled expectation of the inventing community, the decision must come not from the courts, but from Congress.

II. Method Claims

We turn next to Myriad's challenged method claims. The district court's decision predated the Supreme Court's decision in *Bilski*, which rejected this court's machine-or-transformation test as the exclusive test for determining whether an invention is a patent-eligible process under § 101, although the test remains "a useful and important clue." 130 S. Ct. at 3227. Both parties, however, had the opportunity to address the Court's decision in briefing and at oral arguments. Accordingly, we proceed to the merits, and we conclude that all but one of Myriad's method claims are directed to patent-ineligible, abstract mental processes, and fail the machine-or-transformation test.

A. Methods of "Comparing" or "Analyzing" Sequences

Myriad argues that its claims to methods of "comparing" or "analyzing" *BRCA* sequences satisfy the machine-or-transformation test as applied by this court in *Prometheus* because each requires a transformation—extracting and sequencing DNA molecules from a human sample—before the sequences can be compared or analyzed. According to Myriad, the district court failed to recognize the transformative nature of the claims by (1) misconstruing the claim term "sequence" as just information, rather than a physical molecule; and (2) erroneously concluding, in the alternative, that Myriad's proposed transformations were mere data-gathering steps, rather than central to the purpose of the claims.

Plaintiffs respond that these method claims are drawn to the abstract idea of comparing one sequence to a reference sequence and preempt a phenomenon of nature—the correlation of genetic mutations with a predisposition to cancer. And, according to the Plaintiffs, limiting the claims' application to a specific technological field, *i.e.*, *BRCA* gene sequences, is insufficient to render the claims patent eligible. Plaintiffs also assert that the claims do not meet the machine-or-transformation test because the claims' plain language includes just the one step of "comparing" or "analyzing" two gene sequences.

We conclude that Myriad's claims to "comparing" or "analyzing" two gene sequences fall outside the scope of § 101 because they claim only abstract mental processes. *See Benson*, 409 U.S. at 67 ("Phenomena of nature, . . . mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work."). The claims recite, for example, a "method for screening a tumor sample," by "comparing" a first *BRCA1* sequence from a tumor sample and a second *BRCA1* sequence from a non-tumor sample, wherein a difference in sequence indicates an alteration in the tumor sample. '001 patent claim 1. This claim thus recites nothing more than the abstract mental steps necessary to compare two different nucleotide sequences: look at the first position in a first sequence; determine the nucleotide sequence at that first position; look at the first position in a second sequence; determine the nucleotide sequence at that first position; determine if the nucleotide at the first position in the first sequence and the first position in the second sequence are the same or different, wherein the latter indicates an alternation; and repeat for the next position.

Limiting the comparison to just the *BRCA* genes or, as in the case of claim 1 of the '999 patent, to just the identification of particular alterations, fails to render the claimed process patent eligible. As the Supreme Court has held, "the prohibition against patenting abstract ideas 'cannot be circumvented by attempting to limit the use of the formula to a particular technological environment.'" *Bilski*, 130 S. Ct. at 3230 (quoting *Diehr*, 450 U.S. at 191-92); *see also id.* at 3231 ("*Flook* established that limiting an abstract idea to one field of use . . . did not make the concept patentable."). Although the *application* of a formula or abstract idea in a process may describe patentable subject matter, *id.* at 3230, Myriad's claims do not apply the step of comparing two nucleotide sequences in a process. Rather, the step of comparing two DNA sequences is the entire process claimed.

To escape this result, Myriad attempts to read into its method claims additional, transformative steps. As described above, Myriad reads into its claims the steps of (1) extracting DNA from a human sample, and (2) sequencing the *BRCA* DNA molecule, arguing that both steps necessarily precede the step of comparing nucleotide sequences. The claims themselves, however, do not include either of these steps. The claims do not specify any action prior to the step of "comparing" or "analyzing" two sequences; the claims recite just the one step of "comparing" or "analyzing." Moreover, those terms' plain meaning does not include Myriad's proposed sample-processing steps; neither comparing nor analyzing means or implies "extracting" or "sequencing" DNA or otherwise "processing" a human sample.

Myriad claims that "comparing" and "analyzing" take on this meaning when read in light of the patent specifications. Specifically, Myriad argues that the specifications show that the claim term "sequence" refers not to information, but rather to a physical DNA molecule, whose sequence must be determined before it can be compared. We disagree. The patent specifications make clear that "sequence" does not exclusively specify a DNA molecule, but refers more broadly to the linear sequence of nucleotide bases of a DNA molecule. For example, Figure 10A-10H is described as showing the "genomic sequence of BRCA1." '473 patent col.5 l.66. Figure 10 does not show a physical DNA molecule; the figure lists a series of letters (Gs, As, Ts, and Cs) corresponding to the nucleotides guanine, adenine, thymine, and cytosine of a DNA molecule. Similarly, the patent specifications state that "[t]he nucleotide sequence for BRCA1 exon 4 is shown in SEQ ID NO: 11." *Id.* col.53 ll.50-53. SEQ ID NO: 11 again lists a series of Gs, As, Ts, and Cs corresponding to the nucleotide sequence of *BRCA1* exon 4.

Accordingly, Myriad's challenged method claims are distinguishable from the claims upheld under § 101 in *Prometheus*. In *Prometheus*, the patents claimed methods for optimizing the dosage of thiopurine drugs administered to patients with gastrointestinal disorders. 628 F.3d at 1350. As written, the claimed methods included the steps of (a) "administering" a thiopurine drug to a subject, and/or (b) "determining" the drug's metabolites levels in the subject, wherein the measured metabolite levels are compared with predetermined levels to optimize drug dosage. *Id.* In holding that the claims satisfied § 101, this court concluded that, in addition to the "administering" step being transformative, the "determining" step was both transformative and central to the purpose of the claims. *Id.* at 1357. Specifically, the court held that because the metabolite levels could not be determined by mere inspection, the determining step necessarily required a transformation: "Some form of manipulation . . . is necessary to extract the metabolites from a bodily sample and determine their concentration." *Id.* Moreover, we concluded that this transformation was not just insignificant extra-solution activity or necessary data-gathering steps, but was central to the claims, because determining the metabolite levels was what enabled the optimization of drug dosage. *Id.*

Myriad's claims, in contrast, do not include the step of "determining" the sequence of *BRCA* genes by, *e.g.*, isolating the genes from a blood sample and sequencing them, or any other necessarily transformative step. Rather, the comparison between the two sequences can be accomplished by mere inspection alone. Accordingly, Myriad's claimed methods of comparing or analyzing nucleotide sequences fail to satisfy the machine-or-transformation test, and are instead directed to the abstract mental process of comparing two nucleotide sequences. The claims thus fail to claim a patent-eligible process under § 101.

B. Method of Screening Potential Cancer Therapeutics

Lastly, we turn to Myriad's method claim directed to a method for screening potential cancer therapeutics via changes in cell growth rates. '282 patent claim 20. Plaintiffs challenge this claim as directed to the abstract idea of comparing the growth rates of two cell populations and as preempting a basic scientific principle—that a slower growth rate in the presence of a potential therapeutic compound suggests that the compound is a cancer therapeutic. We disagree.

Starting with the machine-or-transformation test, we conclude that the claim includes transformative steps, an "important clue" that it is drawn to a patent-eligible process. *Bilski*, 130 S. Ct. at 3227. Specifically, the claim recites a method that comprises the steps of (1) "growing" host cells transformed with an altered *BRCA1* gene in the presence or absence of a potential cancer therapeutic, (2) "determining" the growth rate of the host cells with or without the potential therapeutic, and (3) "comparing" the growth rate of the host cells. The claim thus includes more than the abstract mental step of looking at two numbers and "comparing" two host cells' growth rates. The claim includes the steps of "growing" transformed cells in the presence or absence of a potential cancer therapeutic, an inherently transformative step involving the manipulation of the cells and their growth medium. The claim also includes the step of "determining" the cells' growth rates, a step that also necessarily involves physical manipulation of the cells. Furthermore, these steps are central to the purpose of the claimed process. *See Prometheus*, 628 F.3d at 1356-57, 1358 (quoting *In re Bilski*, 545 F.3d at 962). The goal of the claim is to assess a compound's potential as a cancer therapeutic, and growing the cells and determining their growth rate is what achieves that goal.

Furthermore, the claim is not so "manifestly abstract" as to claim only a scientific principle, and not a patent-eligible process. *See Research Corp. Techs., Inc. v. Microsoft Corp.*, 627 F.3d 859, 869 (Fed. Cir. 2010). The claim does not cover all cells, all compounds, or all methods of determining the therapeutic effect of a compound. Rather, it is tied to specific host cells transformed with specific genes and grown in the presence or absence of a specific type of therapeutic. Moreover, the claim is tied to measuring a therapeutic effect on the cells solely by changes in the cells' growth rate. The claim thus presents "functional and palpable applications" in the field of biotechnology. *Id.* at 868; *see also Prometheus*, 628 F.3d at 1355 ("[T]he claims do not preempt all uses of the natural correlations; they utilize them in a series of specific steps."). Accordingly, we hold that claim 20 of the '282 patent claims patentable subject matter under § 101.

CONCLUSION

For the foregoing reasons, we affirm the district court's decision to exercise declaratory judgment jurisdiction over this case, we reverse the district court's grant of summary judgment with regard to Myriad's composition claims to isolated DNAs, we affirm the district court's grant of summary judgment with regard to Myriad's method claims to comparing or analyzing gene sequences, and we reverse the district court's grant of summary judgment with regard to Myriad's method claim to screening potential cancer therapeutics via changes in cell growth rates.

AFFIRMED IN PART and REVERSED IN PART

No costs

MOORE, *Circuit Judge*, concurring-in-part.

I join the majority opinion with respect to standing and the patentability of the method claims at issue. I believe, however, that claims directed to isolated DNA sequences present a different set of issues. I join the majority with respect to claims to isolated cDNA sequences, and concur in the judgment with respect to the remaining sequences. I write separately to explain my reasoning.

I.

The Patent Act, 35 U.S.C. § 101, allows "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof" to obtain a patent. The plain language of this statute only requires that an invention be "new and useful," and fall into one of four categories: a "process, machine, manufacture, or composition of matter." Congress did not impose any additional constraints on the scope of patentable subject matter. In fact, "Congress intended statutory subject matter to 'include anything under the sun that is made by man.'" *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) (quoting the statutory history).

While the plain language used by Congress did not limit the scope of patentable subject matter in the statute, the "Court's precedents provide three specific exceptions to § 101's broad patent-eligibility principles: 'laws of nature, physical phenomena, and abstract ideas.'" *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010) (quoting *Chakrabarty*, 447 U.S. at 309). These exceptions "rest[], not on the notion that natural phenomena are not processes [or other articulated statutory categories], but rather on the more fundamental understanding that they are not the kind of 'discoveries' that the statute was enacted to protect." *Parker v. Flook,* 437 U.S. 584, 593 (1978).

Applying the judicially created exception to the otherwise broad demarcation of statutory subject matter in section 101 can be difficult. *See Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 134-45 (1948) (Frankfurter, J., concurring) ("[T]erms as 'the work of nature' and the 'laws of nature' . . . are vague and malleable terms . . . . Arguments drawn from such terms for ascertaining patentability could fairly be employed to challenge almost every patent."). The analysis is relatively simple if the invention previously existed in nature exactly as claimed. For example, naturally existing minerals, a plant found in the wild, and physical laws such as gravity or E=mc2 are not patentable subject matter, even if they were "discovered" by an enterprising inventor. *Chakrabarty*, 447 U.S. at 309.

Even though an invention did not previously exist in nature in exactly the claimed state, however, does not automatically mean it is patentable subject matter. For example, in *Funk Brothers*, the Supreme Court held a patent to a combination of multiple naturally occurring bacterial strains was not patentable. Although there was "an advantage in the combination," which was apparently "new and useful," none of the bacterial strains "acquire[ed] a different use" in combination. *Id.* at 131-32. The aggregation of the bacterial strains into a single product produced "no new bacteria, no change in the six species of bacteria, and no enlargement of the range of their utility. Each species has the same effect it always had. The bacteria perform in their natural way. . . . They serve the ends nature originally provided and act quite independently of any effort of the patentee." *Id.*

In contrast, the Supreme Court held bacteria that included extra genetic material introduced by the inventor were "a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity 'having a distinctive name, character [and] use'" and therefore patentable. *Chakrabarty*, 447 U.S. at 309-310 (quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887)). *Chakrabarty* explained that there is no distinction between inventions based on living and inanimate objects for the purpose of the patent statute; instead, the "relevant distinction" for the section 101 analysis is "between products of nature . . . and human-made inventions." *Id.* at 312-13. Even if the invention was based on nature, and resulted in a living organism, it may fall within the scope of section 101. For example, "the work of the plant breeder 'in aid of nature' was patentable invention" because "'a plant discovery resulting from cultivation is unique, isolated, and is not repeated by nature, nor can it be reproduced by nature unaided by man.'" *Id.* (quoting S. Rep. No. 315, 71st Cong., 2d Sess., 6-8 (1930)). In *Chakrabarty*, the intervention of man resulted in bacteria with "markedly different characteristics" from nature and "the potential for significant utility," resulting in patentable subject matter. *Id.* at 310.

Funk Brothers and *Chakrabarty* do not stake out the exact bounds of patentable subject matter. Instead, each applies a flexible test to the specific question presented in order to determine whether the claimed invention falls within one of the judicial exceptions to patentability. *Funk Brothers* indicates that an invention which "serve[s] the ends nature originally provided" is likely unpatentable subject matter, but an invention that is an "enlargement of the range of . . . utility" as compared to nature may be patentable. 333 U.S. at 131. Likewise, *Chakrabarty* illustrates that an invention with a distinctive name, character, and use, e.g., markedly different characteristics with the potential for significant utility, is patentable subject matter. 447 U.S. at 309-310. Although the two cases result in different outcomes, the inquiry itself is similar.

Courts applied an analogous patentability inquiry long before *Funk Brothers* or *Chakrabarty*. In one notable case, Judge Learned Hand held that purified adrenaline, a natural product, was patentable subject matter. Judge Hand explained that even if the claimed purified adrenaline were "merely an extracted product without change, there is no rule that such products are not patentable." *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95, 103 (S.D.N.Y. 1911). This is because "while it is of course possible logically to call this a purification of the principle" the resulting purified adrenaline was "for every practical purpose a new thing commercially and therapeutically." *Id.* Similarly, in a case applying the Patent Act of 1952,[1] purified vitamin B-12, another natural product, was also held patentable subject matter within the meaning of section 101. *Merck & Co. v. Olin Mathieson Chem. Corp.*, 253 F.2d 156 (4th Cir. 1958). The Fourth Circuit explained that purified vitamin B-12 was "far from the premise of the [naturally occurring] principle. . . . The new product, not just the method, had such advantageous characteristics as to replace the [naturally occurring] liver products. What was produced was, in no sense, an old product." *Id.* at 162-63. These purified pharmaceutical cases are both consistent with Supreme Court precedent: the purified substance was "a new thing . . . therapeutically," *Parke-Davis*, 189 F. at 103, and had such "advantageous characteristics" that what was produced by purification "was, in no sense, an old product." *Merck*, 253 F.2d at 162-63. In other words, the purified natural products were held to have "markedly different characteristics," as compared to the impure products, which resulted in "the potential for significant utility." *Chakrabarty*, 447 U.S. at 310.

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[1] The Patent Act of 1952 was the first time patentable subject matter (the current section 101) was separated out from novelty (the current section 102). Previously, these two concepts were combined into a single section.

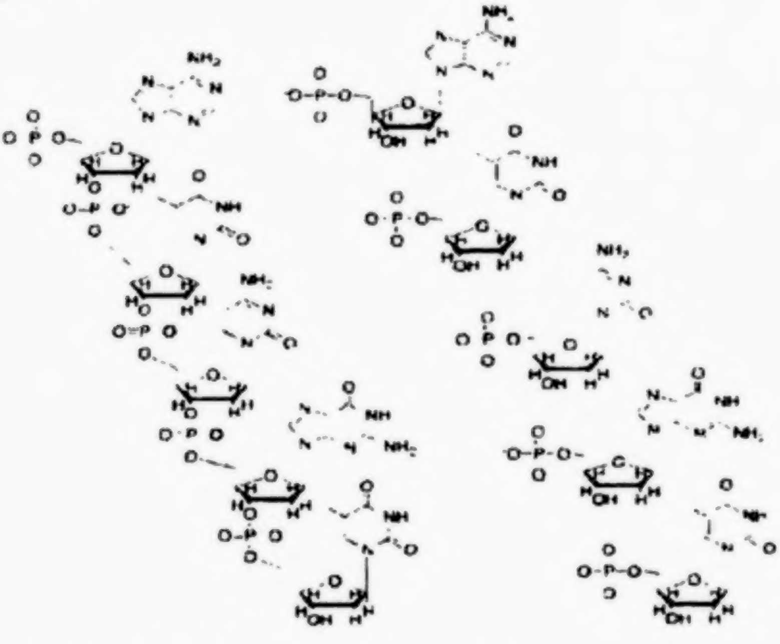
In contrast, mere purification of a naturally occurring element is typically insufficient to make it patentable subject matter. For example, our predecessor court held that claims to purified vanadium and purified uranium were not patentable subject matter since these were naturally occurring elements with inherent physical properties unchanged upon purification. *See In re Marden*, 47 F.2d 958, 959 (CCPA 1931) ("[P]ure vanadium is not new in the inventive sense, and, it being a product of nature, no one is entitled to a monopoly of the same."); *In re Marden*, 47 F.2d 957 (CCPA 1931) ("ductile uranium" not patentable because uranium is inherently ductile). Likewise, claims to purified ductile tungsten were not patentable subject matter since pure tungsten existed in nature and was inherently ductile. *Gen. Elec. Co. v. De Forest Radio Co.*, 28 F.2d 641, 643 (3d Cir. 1928). In each of these cases, purification did not result in an element with new properties. Instead, the court held the naturally occurring element inherently had the same characteristics and utility (e.g. ductility) as the claimed invention. Consistent with *Funk Brothers* and *Chakrabarty*, the claims all fell within the laws of nature exception.

As illustrated by these examples, courts have long applied the principles articulated in *Funk Brothers* and *Chakrabarty* to different factual scenarios in order to determine whether an invention, as claimed, falls into the laws of nature exception. I see no reason to deviate from this longstanding flexible approach in this case. Keeping these principles in mind, I analyze the isolated DNA claims below, to determine whether they have markedly different characteristics with the potential for significant utility, e.g., an "enlargement of the range of . . . utility" as compared to nature. *Chakrabarty*, 447 U.S. at 309-310; *Funk Bros.*, 333 U.S. at 131.

II.

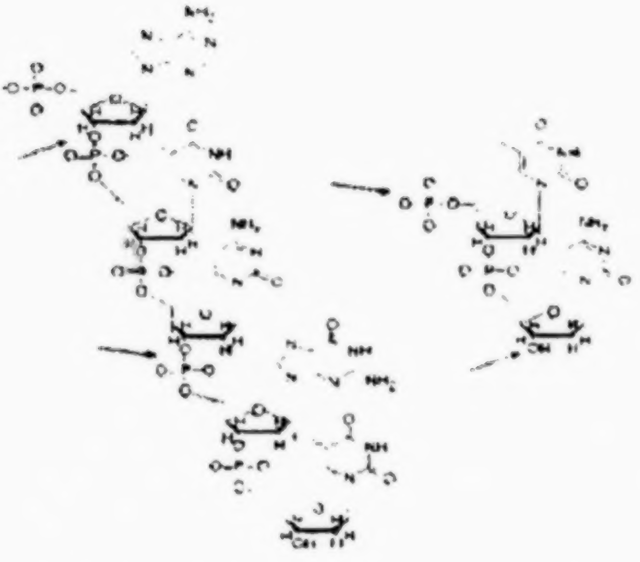
The majority conducts a thoughtful analysis of the scientific principles associated with the claims at issue in this case. I write separately here to emphasize certain chemical considerations which I believe are particularly important in this case.

DNA is a chemical polymer. In principle, a polymeric DNA sequence is no different than any other wellknown polymer, for example, nylon. Like any polymer, DNA is made up of repeating monomer units, connected by chemical bonds to form one larger molecule. In a DNA sequence, the letters A, C, T, and G each represent a different monomer unit; each monomer has a distinct structure, with distinct properties. When they are assembled into a DNA sequence, these monomers are chemically bonded to each other. The process of polymerization of the monomer units—whether carried out by chemical or biological means—results in a new molecule. For example, the sequence A-T-C-G-T represents a single molecule created by polymerizing five monomer units: A, T, C, G, and T again. As illustrated by the figure below, polymerization changes the monomers and results in a molecule with a different ionic charge, different chemical bonds, and a different chemical composition, as compared to the monomers in aggregate.



A-T-C-G-T polymer (left) versus the A, T, C, G, T aggregated monomers (right)

Deconstructing an existing DNA sequence leads to similar results: a fragment of a DNA sequence has different properties than the parent molecule from which it is derived. For example, as shown below, a two nucleotide sequence (T-C), has a different chemical structure, and different chemical connections than the same subunit found within the larger A-T-C-G-T structure. Despite many similarities, it is impossible to find the isolated T-C structure in the A-T-C-G-T molecule. This is because, instead of being connected to a phosphate, the C subunit terminates in a different functional group, a hydroxyl. Likewise, instead of being connected to another sugar via a phosphodiester bond, the T subunit instead terminates in a phosphate. The isolated T-C sequence is a different molecule than the "T-C" sequence appearing as part of the larger A-T-C-G-T polymer. These changes are indicated with arrows below.



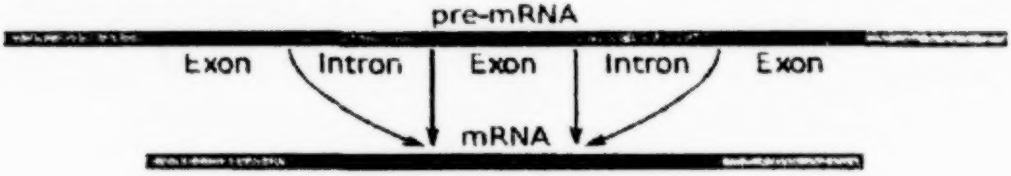
A-T-C-G-T polymer (left, with T-C highlighted) versus "isolated" T-C molecule (right)

The isolated DNA sequences at issue in this case have the same type of chemical changes, but on a much bigger scale. Instead of a string of five nucleotides, the chromosome is millions of base pairs; instead of a two-monomer molecule, the isolated molecules claimed in this case range from 15 nucleotides to thousands (or tens of thousands) of nucleotides. Nevertheless, like the simple sequences discussed above, just because the same series of letters appears in both the chromosome and an isolated DNA sequence does not mean they are the same molecule. While the isolated DNA molecules claimed in this case are undoubtedly inspired by the corresponding naturally occurring sequence present on the chromosome, man must create these isolated DNA molecules. This can be accomplished by building them de novo using chemical or biological means, or by chemically altering the larger polymer to cleave off adjacent portions.

Isolation of a DNA sequence is more than separating out impurities: the isolated DNA is a distinct molecule with different physical characteristics than the naturally occurring polymer containing the corresponding sequence in nature. These differences, of course, are directly related to the change in chemical bonds in the isolated DNA. Instead of being connected to many thousands of additional nucleotides at the 3' and 5' ends of the sequence in question, as is the case in the chromosome, the isolated DNA molecules terminate in, for example, a hydroxyl and a phosphate group, respectively.

There are other differences between an isolated DNA sequence and that same DNA sequence as part of the chromosome. The DNA sequence of a gene, as it occurs in nature, is part of a much larger structure, the chromosome. The claims in suit include DNA sequences as short as fifteen nucleotides, and the isolated BRCA1 cDNA sequence has approximately six thousand nucleotides (see, e.g., '282 col.67-80 (SEQ ID NO:1)). Both of these are much smaller than the isolated full length BRCA1 gene sequence, which, as discussed below, includes both exon and intron sequences. Even the isolated BRCA1 gene, however, is substantially smaller than chromosome 17, which includes the unisolated BRCA1 gene as well as many other genes. J.A. 4321. Isolation of a DNA sequence thus results in a substantially smaller molecule compared to the naturally occurring sequence as part of the chromosome.

cDNA, unlike isolated or unisolated DNA, has a unique sequence of DNA bases (A, C, G, T) which is not actually present in nature. While cDNA is derived from RNA, it has a distinctly different sequence of nucleotides, substituting in the complementary nucleotide (swapping G and C, and A and T/U) to form a DNA sequence that is completely different than the corresponding RNA. There is no contiguous sequence on the chromosome that duplicates the cDNA sequence. Moreover, the naturally occurring gene sequence includes both introns (which are removed) and exons (which are included in the mature RNA). The cDNA sequences, which are complementary to the mature RNA, do not include the introns.



Schematic illustrating RNA splicing (J.A. 4331)

Creating isolated DNA allows a scientist, among other things, to remove potentially confounding sequences that are naturally present in the larger chromosomal polymer, and instead focus on just the sequence of interest. This aspect of isolated DNA has important practical consequences and leads to additional utility, particularly for the smaller isolated fragments. For example, a small fragment of isolated DNA can be used as a primer in order to selectively detect the presence of the BRCA1 gene or BRCA1 gene mutation in a patient. Armed with this scientific background, we can now apply the principles of *Funk Brothers* and *Chakrabarty* to the isolated DNA claims at issue.

III.

The isolated DNA claims of the patents in suit fall into two categories. The first category of claims is directed to isolated sequences that are identical to naturally occurring gene sequences. These include claims encompassing both the isolated full length gene sequence (e.g. claim 1 of '282 patent), which are thousands of nucleotides, and claims to shorter isolated DNA strands, with as few as fifteen nucleotides, whose nucleotide sequence is found on the chromosome (e.g. claim 5 of '282 patent). The second category of claims is directed to isolated DNA sequences that are different from the naturally occurring gene sequences. These include claims to isolated cDNA molecules (e.g. claim 2 of the '282 patent), which differ from the natural gene sequence in that the introns are removed, and are the opposite (complementary) sequence of the naturally occurring RNA.

The cDNA claims present the easiest analysis. Although the plaintiffs (now plaintiff) in the suit argue, and the district court held, that cDNA falls within the "laws of nature" exception to section 101 patentability, I cannot reconcile this argument with the fact that the claimed cDNA sequences do not exist in nature. Moreover, since cDNA has all of the introns removed, and only contains the coding nucleotides, it can be used to express a protein in a cell which does not normally produce it. Of course, the claimed isolated cDNA is inspired by nature—after all, naturally occurring RNA is the template upon which cDNA is constructed. Because it is used as a template, however, cDNA has a complementary sequence of nucleotides, and therefore has a completely different nucleotide sequence than the RNA. Moreover, DNA has a different chemical structure than RNA, including a different base (T instead of U, respectively) and sugar units (deoxyribose instead of ribose, respectively). This results in, among other things, greater stability for the DNA sequence as compared to the RNA sequence.

cDNA sequences thus have a distinctive name, character, and use, with markedly different chemical characteristics from either the naturally occurring RNA or any continuous DNA sequence found on the chromosome. The claimed isolated cDNA sequences are the creation of man, made using biological tools and the naturally occurring mRNA as a template. cDNA is therefore not one of the "'manifestations of . . . nature, free to all men and reserved exclusively to none'" that falls outside of the patent system. *Chakrabarty*, 447 U.S. at 309 (quoting *Funk Bros.*, 333 U.S. at 130). I decline to extend the laws of nature exception to reach entirely manmade sequences of isolated DNA, even if those sequences are inspired by a natural template. I therefore join the majority opinion with respect to the claims to cDNA sequences.[2]

DNA sequences that have the same pattern of DNA bases as a natural gene, in whole or in part, present a more difficult issue. Unlike the isolated cDNA molecules, whose sequence is not present in nature, these kinds of isolated DNA claims include nucleotide sequences which are found in the human body, albeit as part of a much larger molecule, the chromosome. The majority analysis focuses on the "markedly different chemical structure" of isolated DNAs, as compared to the corresponding native DNA. Majority at 45. Although the different chemical structure does suggest that claimed DNA is not a product of nature, I do not think this difference alone necessarily makes isolated DNA so "markedly different," *Chakrabarty*, 447 U.S. at 310, from chromosomal DNA so as to be per se patentable subject matter. *Cf. Funk Bros.*, 333 U.S. at 130-31 (Creation of "a new and different composition" of bacterial strains was nevertheless not patentable subject matter).

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[2] To the extent the claims to shorter portions of cDNA include only naturally occurring sequences found in the chromosome, for example claim 6 of the '282 patent, my reasoning is the same as for the isolated sequences of claim 5, discussed below.

Given the chemical differences highlighted by Judge Lourie's opinion and discussed *supra*, the mere fact that the larger chromosomal polymer includes the same sequence of nucleotides as the smaller isolated DNA is not enough to make it per se a law of nature and remove it from the scope of patentable subject matter. The actual molecules claimed in this case are therefore not squarely analogous to unpatentable minerals, created by nature without the assistance of man. Instead, the claimed isolated DNA molecules, which are truncations (with different ends) of the naturally occurring DNA found as part of the chromosome in nature, are not naturally produced without the intervention of man. *Cf. Chakrabarty*, 447 U.S. at 312-13.

Given the differences, we should, as precedent instructs, consider whether these differences impart a new utility which makes the molecules markedly different from nature. I begin with the short isolated sequences such as those covered by claim 5 which is directed to "an isolated DNA having at least 15 nucleotides of the DNA of claim 1." This claim covers a sequence as short as 15 nucleotides and arguably as long as the entire gene. For this claim to be patent eligible, all of the sequences ranging from the 15 nucleotide sequence to the full gene must be patentable subject matter. The shorter isolated DNA sequences have a variety of applications and uses in isolation that are new and distinct as compared to the sequence as it occurs in nature. For example, these sequences can be used as primers in a diagnostic screening process to detect gene mutations. These smaller isolated DNA sequences—including isolated radiolabeled sequences mirroring those on the chromosome—can also be used as the basis for probes. Naturally occurring DNA cannot be used to accomplish these same goals. Unlike the isolated DNA, naturally occurring DNA simply does not have the requisite chemical and physical properties needed to perform these functions.

The ability to use isolated DNA molecules as the basis for diagnostic genetic testing is clearly an "enlargement of the range of . . . utility" as compared to nature. *Funk Bros.*, 333 U.S. at 131. Indeed, many of the plaintiffs in this case submitted declarations indicating that they wanted to either offer such testing or receive such testing. These new applications, of course, rely on physical properties devised by nature, namely the ability of a strand of DNA to specifically interact with a complementary strand. Diagnostic testing, however, is not a natural utility—the body does not naturally engage in this type of testing, and certainly does not do so with the shorter (non-naturally occurring) isolated DNA used by man. As such, the claimed DNA does not "serve the ends nature originally provided." *Id.* Instead, the isolated DNA sequences have markedly different properties which are directly responsible for their new and significant utility. *Chakrabarty*, 447 U.S. at 309-10. The same sequence, as it appears in nature as part of the chromosome, simply cannot be used in the same way. Because the different chemical structure of the isolated DNA, which is a product of the intervention of man, leads to a different and beneficial utility, I believe small, isolated DNA fragments are patentable subject matter.

In fact, much of the dissent's analysis with regard to the full gene would seem to support my conclusion that small isolated DNA molecules are directed to patent-eligible subject matter. The dissent explains why the baseball bat is directed to patent eligible subject matter: "man has defined the parts that are to be retained and the parts that are to be discarded. The result of the process of selection is a product with a function that is entirely different from that of the raw material from which it was obtained." Dissent at 11. The exact same thing is true with regard to primer and probe claims. Man has whittled the chromosomal DNA molecule down to a 15 nucleotide sequence—defining the parts to be retained and discarded. And the result is a product with a function (primer or probe) that is entirely different from the full gene from which it was obtained.[3] I conclude that the small, isolated DNA molecules, are an alteration of the natural product "with markedly different characteristics from any found in nature and one having the potential for significant utility." *Chakrabarty*, 447 U.S. at 310.

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[3] The dissent analogizes the full BRCA gene to a slab of marble found in the earth as distinct from the sculpture carved into it, which the dissent indicates would be worthy of intellectual property protection. If the multi-thousand nucleotide BRCA gene is the slab, isn't the 15 nucleotide primer the sculpture?

Longer strands of isolated DNA, in particular isolated strands which include most or all of the entire gene, are a much closer case. Some of the claims at issue, for example '282 patent claim 5, are genus claims, drafted broadly enough to include both short fragments as well as the entire isolated gene sequence. As discussed above, I believe many species within this genus—the shorter isolated DNA fragments—are clearly patentable subject matter based on their new structure and corresponding enlarged range of utility. Yet that still leaves species that include most or all of the isolated gene sequence. While I ultimately conclude that these longer isolated sequences, including the isolated gene sequence as a whole, are also patentable subject matter, I do so for a reason different than for the shorter sequences.

All of the same structural arguments apply to any length of isolated DNA so, like the shorter strands, an isolated DNA coding for a gene does have a literal chemical difference from the gene as it appears on the chromosome. Different ends in a 15 nucleotide sequence have greater significance than different ends in a 6000 nucleotide sequence. Unlike the shorter strands of isolated DNA, the chemical and structural differences in the isolated gene do not clearly lead to an "enlargement of the range of . . . utility" as compared to nature. *Funk Bros.*, 333 U.S. at 131. For example, the full length gene is too large to be used as a probe. *See* J.A. 4322 (a probe is a

DNA molecule usually 100-1,000 bases long). Likewise, an entire isolated gene appears unsuitable for use as a primer in genetic screening for mutations in that same gene. *See* J.A. 4323 (Primers "are complementary to an exact location of a *much larger target* DNA molecule." (emphasis added)). As such, the chemical and structural differences in an isolated DNA sequence which includes most or all of a gene do not clearly lead to significant new utility as compared to nature. Whether an isolated gene is patentable subject matter depends on how much weight is allocated to the different structure as compared to the similarity of the function to nature.

If I were deciding this case on a blank canvas, I might conclude that an isolated DNA sequence that includes most or all of a gene is not patentable subject matter. Despite the literal chemical difference, the isolated full length gene does not clearly have a new utility and appears to simply serve the same ends devised by nature, namely to act as a gene encoding a protein sequence. This case, however, comes to us with a substantial historical background.

Congress has, for centuries, authorized an expansive scope of patentable subject matter. Likewise, the United States Patent Office has allowed patents on isolated DNA sequences for decades, and, more generally, has allowed patents on purified natural products for centuries. There are now thousands of patents with claims to isolated DNA, and some unknown (but certainly large) number of patents to purified natural products or fragments thereof.[4] As I explain below, I believe we must be particularly wary of expanding the judicial exception to patentable subject matter where both settled expectations and extensive property rights are involved. Combined with my belief that we should defer to Congress, these settled expectations tip the scale in favor of patentability.[5]

IV.

For more than a decade the Patent Office's policy has been that "[a]n isolated and purified DNA molecule that has the same sequence as a naturally occurring gene is eligible for a patent because . . . that DNA molecule does not occur in that isolated form in nature . . . ." 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001). The explicit statement of the Patent Office's position on isolated DNA, however, is simply a continuation of a longstanding and consistent policy of allowing patents for isolated natural products. *See id.* (noting U.S. Patent 141,072, claiming "[y]east, free from organic germs of disease," issued to Louis Pasteur in 1873); *cf. In re Bergstrom*, 427 F.2d 1394 (CCPA 1970) (isolated prostaglandins patentable). According to the Patent Office, isolated DNA is no different from the isolated natural products of *Parke-Davis. See* 66 Fed. Reg. at 1093 (quoting *Parke-Davis*).

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[4] *See, e.g.*, U.S. Patent 3,067,099 (claiming vancomycin, an antibiotic produced by bacteria found in soil) and U.S. Patent 4,552,701 (claiming a vancomycin fragment produced by removing a sugar unit). A natural product fragment, for example a naturally occurring antibiotic with a sugar moiety removed, is highly analogous to isolated DNA. In each case, the claimed molecule is a smaller fragment of a naturally occurring molecule, with some naturally occurring functionality removed. *See* U.S. Patent 4,552,701, col.3-4 (compare entry 2 with entries 10 and 13).

[5] My analysis of the claims at issue assumes that they do not include an isolated, full length chromosome. I do not believe that a claim to an entire chromosome, for example chromosome 17, is patentable subject matter. First, there is no indication that the chromosome in isolation has markedly different characteristics compared to the chromosome in nature. Second, unlike claims to isolated genes, there is no indication of either settled expectations or extensive property rights for claims to isolated chromosomes. This is undoubtedly due to the small number of chromosomes as compared to the number of genes.

Even before the current guidelines formalized the Patent Office's position, however, it granted patents to human genes in the early 1980s, and subsequently issued thousands of patents on "isolated DNA." Majority at 48. In fact, claims similar to the ones at issue in this case have been the focal point of important litigation. For example, *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200 (Fed. Cir. 1991), involved a claim to "'[a] purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.'" *Id.* at 1203-04 (quoting U.S. Patent No. 4,703,008, claim 2). We affirmed that this claim was valid and infringed. *Id.* at 1219. Erythropoietin, also known as EPO, went on to become the biggest-selling biotechnology drug developed to that point, resulted in billions of dollars in sales, and accounted for over 50% of Amgen's revenue in 1997. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 77 (D. Mass. 2001). Isolated DNA claims, at least in the case of Amgen, represent crucial and exceedingly valuable property rights.

The settled expectations of the biotechnology industry—not to mention the thousands of issued patents—cannot be taken lightly and deserve deference. This outpouring of scientific creativity, spurred by the patent system, reflects a substantial investment of time and money by the biotechnology industry to obtain property rights related to DNA sequences. The type of fundamental alteration in the scope of patentable subject matter argued in this case "risk[s] destroying the legitimate expectations of inventors in their property." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002). I believe leaving intact the settled expectations of property owners is particularly important in light of the large number of property rights involved, both to isolated DNA and to purified natural products generally.

The Supreme Court has warned that "courts must be cautious before adopting changes that disrupt the settled expectations of the inventing community." *Festo*, 535 U.S. at 739. The settled expectations of the inventing community with respect to isolated DNA claims are built upon the broad language of the statute, judicial precedent, such as *Parke-Davis* and *Merck*, and the Patent Office's longstanding policy and practice. Neither *Funk Brothers* nor *Chakrabarty* purported to overrule either the early cases or the Patent Office's practice; indeed, as discussed *supra*, these cases weigh the same considerations as *Parke-Davis* and *Merck*. "'To change so substantially the rules of the game now,'" after more than a century of practice, "'could very well subvert the various balances the PTO sought to strike when issuing the numerous patents which have not yet expired and which would be affected by our decision.'" *Festo*, 535 U.S. at 739 (quoting *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 32 n.6 (1997)).

Although the Patent Office has consistently followed the same policy for a decade (and arguably a century or more), the United States, as an amicus represented at argument by the Solicitor General, now argues that the Patent Office's published guidelines are incorrect and a misstatement of the law. In place of these guidelines, the Solicitor General suggested that we should use a "magic microscope" as part of our section 101 analysis. If we could observe the claimed substance in nature using this microscope, the Solicitor General argues, it is not patentable. The magic microscope test applies equally to portions of a larger, naturally occurring molecule. For example, the optical field of view could be zoomed to see just a sequence of fifteen nucleotides within the chromosome. As long as you could "see" the claimed molecule in nature using the magic microscope, it would fall into the "laws of nature" exception and be unpatentable subject matter.

Certainly the magic microscope has curb appeal—its child-like simplicity an apparent virtue. The magic microscope, however, would not see the claimed DNA molecules at issue in this case. An isolated DNA molecule has different chemical bonds as compared to the "unisolated" sequence in the chromosome (the ends are different). In short, the claimed molecules cannot be seen in nature through the magic microscope. While you may be able to see the order of DNA nucleotides in the chromosome, the isolated fragment of DNA is a different molecule. It may be that the microscope can also break and form chemical bonds to yield the claimed isolated DNA. Even so, the microscope must make some decisions: should the isolated DNA begin and end in a phosphate? a hydrogen? a hydroxyl? a methyl group? an acyl group? These decisions might be obvious to a person of ordinary skill in the art, but they are not inherent to the unisolated sequence as part of the chromosome. Creating the claimed isolated DNA sequences therefore results in a distinctly unnatural molecule.[6] Even the dissent agrees that the isolated DNA molecules at issue require cleaving chemical bonds, though it disputes the importance of the resulting distinct "'molecular species.'" Dissent at 7 (quoting Linus Pauling, *The Nature of the Chemical Bond* 6 (3d ed. 1960)). The magic microscope test simply does not work the way the government claims.

While the magic microscope creates a bright line rule, it presents a poorly defined question: can we "see" the claimed molecule, or something fairly similar, in nature? Even if the scientific imprecision of the test were excusable, the government also asks us to do away with *Chakrabarty's* flexible inquiry as to whether the invention, as claimed, has "markedly different characteristics from any found in nature" which result in "the potential for significant utility." *Id.* at 310. Indeed, the bright line magic microscope test actually appears to be contrary to *Funk Brothers*, since the combination of bacteria in that case was a "new and different composition of non-inhibitive strains," 333 U.S. at 130-31, and therefore not actually present in nature. There may be additional nuance in the government's argument that accounts for this inconsistency, but under my understanding of the magic microscope test, the combination in *Funk Brothers* would be patentable subject matter.

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[6] This also illustrates why the government's analogies to situations dealing with elements, for example lithium, are inapposite. Even assuming the government's contention that lithium does not exist in isolated form in nature, it is nevertheless clear that elemental lithium, a basic building block provided by nature, at some point must have reacted with, e.g., water to form the naturally occurring lithium salts. In contrast, an isolated DNA sequence did not necessarily exist before reacting further to produce the corresponding naturally occurring chromosomal DNA. Unlike a lithium salt, the chromosome does not imply that an isolated DNA molecule of 15 nucleotides—or even a gene—necessarily previously existed as an isolated molecule in nature.

Indeed, the government does not apply its own understanding of section 101 consistently. In its brief, the United States explains that "[a] chemical alteration of a bioactive molecule to improve absorption by the body . . . would likely satisfy section 101." United States Amicus Br. 31 n.8. As discussed *supra*, the isolated DNA molecules at issue in this case are the result of a "chemical alteration of a bioactive molecule" that leads to different properties, including a dramatic reduction in size. Just as the government's theoretical "chemical alteration" leads to a molecule with improved absorption properties, the isolation of discrete DNA sequences changes the properties of the sequence as compared to the chromosomal DNA. This is not "[m]erely sorting the proverbial wheat from the chaff," *id.*, but the creation of new DNA molecules with distinct properties and additional utility, including the ability to be used as a primer in genetic testing.[7]

Also troubling is the apparent lack of awareness about the impact of the proposed test. The government asserts that the magic microscope "is a very limited position"; the government is wrong. This test cannot be limited to DNA by either legal or scientific principles. For example, Louis Pasteur's 1873 claim to "Yeast, free from organic germs of disease, as an article of manufacture" runs afoul of the magic microscope since the microscope could zoom in to see that yeast free from contaminants. Similarly, isolated naturally occurring molecules long considered patentable subject matter, including adrenaline, vitamin B-12, and prostaglandins, would also fall outside the scope of section 101. Although the powers of the magic microscope are not entirely clear, it appears that patents to smaller fragments of naturally occurring molecules, for example claims to truncated proteins (*see, e.g.*, U.S. Patent No. 4,762,914, entitled "Truncated Protein of Interleukin-1"), would also be unpatentable.

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[7] The government's position may be that adding functionality to a naturally occurring molecule, for example adding a lipid chain, is a creation of man while removing functionality, for example truncating a natural DNA sequence or protein to yield smaller molecules with new properties, is not. Scientifically, this distinction makes little sense: in either case, it is the intervention of man that created a new molecule. After all, the hand of man is just as apparent in the David, created by removing stone from a block of marble, as the ceiling of the Sistine Chapel, created by adding layers of paint to an existing structure.

The government's new test fundamentally changes more than a century of precedent and Patent Office practice in the pharmaceutical and biotechnology arena. The proposed test is a purely mechanical inquiry that fails to account for the possibility that chemical changes to the isolated DNA sequences at issue, as compared to their natural state, could result in markedly different uses. As such, the government's position in this case calls into question the validity of an unknown number of patents and claims and upsets the settled expectations of some of our most innovative industries. This is not a "very limited position."

The dissent claims that the Patent Office's past views are "substantially undermined by the position the government has taken in this case." Dissent at 18. The Patent Office's prior practice, however, is particularly important since it resulted in a large number of property rights over the past decades. If the Executive decided to change course in the Patent Office, and decline to issue new patents to isolated genes, it would not impact these existing property rights. This, however, is not what the Executive argues in this case. Instead the Solicitor General argues for an entirely different interpretation of the law that would destroy existing property rights. Although the dissent points out that *Chakrabarty* overturned the Patent Office's practice of denying patents to microorganisms, there is a clear difference between allowing additional patent protection where none previously existed, and denying patent protection decades (or centuries) after the fact, thereby eliminating a large number of property rights. Moreover, *Chakrabarty*, consistent with the broad language of the statute, allowed additional patents where none previously existed. Here, the Solicitor General proposes to destroy existing property rights based on a judge made exception to that same broad language. This is a dramatic step that I believe is best left to the legislature.

Nevertheless, the Solicitor General claims that "this is a pure question of law" and that we can therefore feel free to ignore the years of Patent Office practice and the accompanying expectations that practice created within the industry. The Solicitor General argues that we should not defer to the broad language (all but unchanged since 1793) provided by Congress in the patent statute, or allow Congress to decide whether it is necessary to correct the Patent Office's practice through legislation. It is tempting to use our judicial power in this fashion, especially when the patents in question raise substantial moral and ethical issues related to awarding a property right to isolated portions of human DNA—the very thing that makes us humans, and not chimpanzees.

The Solicitor General's invitation is tempting, but I must decline the opportunity to act where Congress remains silent. "[O]ur obligation is to take statutes as we find them . . . ." *Chakrabarty*, 447 U.S. at 315. With respect to section 101, "[t]he subject-matter provisions of the patent law have been cast in broad terms to fulfill the constitutional and statutory goal of promoting 'the Progress of Science and the useful Arts' . . . ." *Id.* Any judicial exception to the statute's broad language must be applied with care lest the courts usurp Congress's constitutionally mandated authority to promote science and useful arts. Judicial restraint is particularly important here because an entire industry developed in the decades since the Patent Office first granted patents to isolated DNA. Disturbing the biotechnology industry's settled expectations now risks impeding, not promoting, innovation.

Regardless, the judiciary is illsuited to determine whether the claims at issue promote or inhibit science and useful arts in all but the clearest cases, for example a new mineral discovered in the earth, or a new plant found in the wild, or E=mc2, or the law of gravity. Instead, I leave it to Congress, who "has the constitutional authority and the institutional ability to accommodate fully the varied permutations of competing interests that are inevitably implicated by such new technology," *Sony Corp. of America v. Universal City Studios, Inc.*, 464 U.S. 417, 431 (1984), to decide whether it is necessary to change the scope of section 101 to exclude the kind of isolated DNA claims at issue here. "[U]ntil Congress takes such action, this [c]ourt must construe the language of § 101 as it is." *Chakrabarty*, 447 U.S. at 318. Section 101 is, on its face, broad enough to include the claims to isolated DNA at issue here.

The dissent suggests that "this may well be one of those instances in which 'too much patent protection can impede rather than 'promote the Progress of Science and useful Arts.'" Dissent at 17 (quoting *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 126 (2006) (Breyer, J., dissenting from dismissal of writ as improvidently granted)). Yet the biotechnology industry is among our most innovative, and isolated gene patents, including the patents in suit, have existed for decades with no evidence of ill effects on innovation. *See* David E. Adelman & Kathryn L. DeAngelis, *Patent Metrics: The Mismeasure of Innovation in the Biotech Patent Debate*, 85 Tex. L. Rev. 1677, 1681 (2007) ("The existing empirical studies find few clear signs that the patenting of biotechnology inventions is adversely affecting biomedical innovation."); *id.* at 1729 (concluding "that overall biotechnology innovation is not being impaired by the growth in patents issued"). Changing course years after the fact will only serve to punish those companies who made the reasonable decision to invest large amounts of time and money into the identification, isolation, and characterization of genes. Unsettling the expectations of the biotechnology industry now, based on nothing more than unsupported supposition, strikes me as far more likely to impede the progress of science and useful arts than advance it. Given the complicated technology and conflicting incentives at issue here, any change must come from Congress. *See Gottschalk v. Benson*, 409 U.S. 63, 72-73 (1972) (A section 101 analysis raises "considerable problems . . . which only committees of Congress can manage, for broad powers of investigation are needed, including hearings which canvass the wide variety of views which those operating in this field entertain. The technological problems tendered [by the parties] . . . indicate to us that considered action by the Congress is needed.").

In fact, Congress has at least implicitly approved of the Patent Office's policy of awarding patents on genes and DNA sequences. For example, Congress included, as part of the Patent Office's appropriations, language affirming the Patent Office's interpretation of section 101 to prohibit patents on human organisms. Consolidated Appropriations Act, 2004, Pub. L. No. 108-199, § 634, 118 Stat. 3, 101. Although Congress was aware "that there are many institutions . . . that have extensive patents on human genes," 149 Cong. Rec. H7248, H7274, it explicitly declined to implement legislation to "affect any of those current existing patents." *Id.* (statement of Mr. Weldon introducing amendment). To the contrary, it made clear that the language related to "human organisms" was not intended to change the Patent Office's policy with respect to claims to genes, stem cells, or other similar inventions. *Id.*[8] Far from oblivious to the patenting of genes, members of Congress previously introduced bills which would put a moratorium on gene patents,[9] authorize funding for the study of whether genes ought to be patentable,[10] and exempt from patent infringement anyone who uses patented genes for non-commercial research purposes or medical practitioners who use genetic diagnostic tests.[11] None of these became law. Congress is obviously aware of the issues presented in this case and I believe "[a]ny recalibration of the standard of [patentability] remains in its hands." *Microsoft Corp. v. i4i Ltd.*, 131 S.Ct. 2238, 2252 (2011).

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[8] *See also* 149 Cong. Rec. E2417-01 ("What I want to point out is that *the U.S. Patent Office has already issued patents on genes*, stem cells, animals with human genes, and a host of non-biologic products used by humans, but it has not issued patents on claims directed to human organisms, including human embryos and fetuses. *My amendment would not affect the former*, but would simply affirm the latter.") (emphasis added) (statement of Mr. Weldon after amendment approved); *see also* 157 Cong. Rec. E1177-04 (resubmitting this testimony in the context of the current patent reform legislation).

[9] At least one bill was introduced in Congress to put a moratorium on patents to human genes or gene sequences. *See, e.g.*, The Animal and Gene Patent Moratorium Bill (S.387 1993).

[10] The Genomic Science and Technology Innovation Act of 2002 (H.R. 3966).

This case typifies an observation by the late Chief Judge Markey, our first Chief Judge, that "[o]nly God works from nothing. Men must work with old elements." *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 n.3 (Fed. Cir. 1985) (quotation, citations omitted). Human DNA is, for better or worse, one of the old elements bequeathed to men to use in their work. The patents in this case revealed a new molecular understanding about ourselves; "the inventions most benefiting mankind are those that 'push back the frontiers of chemistry, physics, and the like.'" *Chakrabarty*, 447 U.S. at 316 (quoting *Great A. & P. Tea Co. v. Supermarket Corp.*, 340 U.S. 147, 154 (1950)). We cannot, after decades of patents and judicial precedent, now call human DNA fruit from the poisonous tree, and punish those inquisitive enough to investigate, isolate, and patent it. "Our task . . . is the narrow one of determining what Congress meant by the words it used in the statute; once that is done our powers are exhausted." *Id.* at 318. This inquiry does not have moral, ethical, or theological components. *Cf. id.* at 316-17 ("[W]e are without competence to entertain" arguments about "the grave risks" generated by genetic research.). The patents in this case might well deserve to be excluded from the patent system, but that is a debate for Congress to resolve. I therefore decline to extend the "laws of nature" exception to include isolated DNA sequences.

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[11] The Genomic Research and Diagnostic Accessibility Act of 2002 (H.R. 3967). As the bill's sponsor explained: "It is important to note that this section would not overturn the commercial rights of patent holders. If a research [organization] utilizing the exemption makes a commercially viable finding, he or she would still have to negotiate any rights to market the new discovery with the patent holder." 148 Cong. Rec. E353-03.

BRYSON, *Circuit Judge*, concurring in part and dissenting in part:

I concur with the portions of this court's judgment that are directed to standing, the patentability of the cDNA claims, and the patentability of the method claims. I respectfully dissent, however, from the court's holding that Myriad's BRCA gene claims and its claims to gene fragments are patent-eligible. In my view, those claims are not directed to patentable subject matter, and if sustained the court's decision will likely have broad consequences, such as preempting methods for whole-genome sequencing, even though Myriad's contribution to the field is not remotely consonant with such effects.

In its simplest form, the question in this case is whether an individual can obtain patent rights to a human gene. From a commonsense point of view, most observers would answer, "Of course not. Patents are for inventions. A human gene is not an invention." The essence of Myriad's argument in this case is to say that it has not patented a human gene, but something quite different—an *isolated* human gene, which differs from a native gene because the process of extracting it results in changes in its molecular structure (although not in its genetic code). We are therefore required to decide whether the process of isolating genetic material from a human DNA molecule makes the isolated genetic material a patentable invention. The court concludes that it does; I conclude that it does not.

At the outset, it is important to identify the inventive contribution underlying Myriad's patents. Myriad was not the first to map a BRCA gene to its chromosomal location. That discovery was made by a team of researchers led by Dr. Mary-Claire King. *See* Jeff M. Hall et al., *Linkage of Early-Onset Familial Breast Cancer to Chromosome 17q21*, 250 Science 1684 (1990). And Myriad did not invent a new method of nucleotide sequencing. Instead, it applied known sequencing techniques to identify the nucleotide order of the BRCA genes.[1] Myriad's discovery of those sequences entailed difficult work, and the identified sequences have had important applications in the fight against breast cancer. But the discovery of the sequences is an unprotectable fact, just like Dr. King's discovery of the chromosomal location of the BRCA1 gene.

Of course, Myriad is free to patent applications of its discovery. As the first party with knowledge of the sequences, Myriad was in an excellent position to claim applications of that knowledge. Many of its unchallenged claims are limited to such applications. *See, e.g.*, '441 patent, claim 21; '492 patent, claim 22; '282 patent, claim 9. Yet some of Myriad's challenged composition claims effectively preempt any attempt to sequence the BRCA genes, including whole-genome sequencing. In my view, those claims encompass unpatentable subject matter, and a contrary ruling is likely to have substantial adverse effects on research and treatment in this important field.

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[1] There is some dispute over whether other inventors helped Myriad discover the BRCA sequences or discovered the BRCA2 sequence before Myriad. Because those disputes are irrelevant to the question of patentable subject matter, I refer to the discovery of the BRCA sequences as Myriad's work.

I.

As the majority and concurring opinions explain, the claims at issue in this case fall into three categories: claims that cover the isolated BRCA genes (claim 1 of the '282 patent, claim 1 of the '473 patent, and claims 1 and 6 of the '492 patent); claims that cover only the BRCA cDNA (claims 2 and 7 of the '282 patent and claim 7 of the '492 patent); and claims that cover portions of the BRCA genes and cDNA as small as 15 nucleotides long (claims 5 and 6 of the '282 patent). I first address the claims to the BRCA genes.

A.

In the seminal case of *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), the Supreme Court held that an artificial life form could be patented. In the course of its opinion, and critically for purposes of its reasoning, the Court stated that not all living things or other items found in nature were subject to patenting. The Court explained that although the language of section 101 of the Patent Act is broad, it is not the case that it "has no limits or that it embraces every discovery." *Id.* at 309. The Court then set forth the general proposition that "laws of nature, physical phenomena, and abstract ideas have been held not patentable." *Id.* As examples, the Court noted that "a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter." Thus, even though a mineral or a plant is a "composition of matter," and could be viewed as falling within a broad construction of section 101, the Court explained that those "manifestations of . . . nature" are not patentable subject matter, but are "free to all men and reserved exclusively to none." *Id.*, quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948); *see also Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010).

The Court in *Chakrabarty* held the artificial life form at issue in that case to be patentable because the claim was "not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity 'having a distinctive name, character [and] use.'" *Id.* at 309-10, quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887). In distinguishing between naturally occurring substances and nonnaturally occurring manufactures, the Court relied heavily on its earlier decision in *Funk Brothers*, in which the inventor discovered that certain useful bacterial strains did not exert an inhibitive effect on each other. Based on that discovery, the inventor obtained a patent on a mixed culture of those non-inhibitive strains. The Supreme Court held the product unpatentable, however, because the bacteria remained structurally and functionally the same as in their natural state. *Funk Bros.*, 333 U.S. at 131. By contrast, because Chakrabarty had produced "a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility," the Court held Chakrabarty's invention to be patentable. *Chakrabarty*, 447 U.S. at 310.

B.

Myriad's claims to the isolated BRCA genes seem to me to fall clearly on the "unpatentable" side of the line the Court drew in *Chakrabarty*. Myriad is claiming the genes themselves, which appear in nature on the chromosomes of living human beings. The only material change made to those genes from their natural state is the change that is necessarily incidental to the extraction of the genes from the environment in which they are found in nature. While the process of extraction is no doubt difficult, and may itself be patentable, the isolated genes are not materially different from the native genes. In this respect, the genes are analogous to the "new mineral discovered in the earth," or the "new plant found in the wild" that the Supreme Court referred to in *Chakrabarty*. It may be very difficult to extract the newly found mineral or to find, extract, and propagate the newly discovered plant. But that does not make those naturally occurring items the products of invention.

The same is true for human genes. Like some minerals, they are hard to extract from their natural setting. Also like minerals, they can be used for purposes that would be infeasible if they remained in their natural setting. And the process of extracting minerals, or taking cuttings from wild plants, like the process of isolating genetic material, can result in some physical or chemical changes to the natural substance. But such changes do not make extracted minerals or plant cuttings patentable, and they should not have that effect for isolated genes. In each case, merely isolating the products of nature by extracting them from their natural location and making those alterations attendant to their extraction does not give the extractor the right to patent the products themselves.

The majority characterizes the isolated genes as "new molecules" and considers them different substances from the corresponding native DNA.[2] Because the native BRCA genes are chemically bonded to other genes and histone proteins, the majority concludes that cleaving those bonds to isolate the BRCA genes turns the isolated genes into "different materials." Yet there is no magic to a chemical bond that requires us to recognize a new product when a chemical bond is created or broken, but not when other atomic or molecular forces are altered.[3] A chemical bond is merely a force between two atoms or groups of atoms strong enough "to make it convenient for the chemist to consider [the aggregate] as an independent molecular species." Linus Pauling, *The Nature of the Chemical Bond* 6 (3d ed. 1960). Weaker interatomic forces will be broken when, for example, a dirty diamond is cleaned with water or another solvent, but that does not make the clean diamond a human-made invention. *See Am. Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S.

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[2] Although I recognize that Judge Lourie and Judge Moore, while reaching the same ultimate conclusions, have taken analytical paths that differ in some respects, for convenience I will refer to Judge Lourie's opinion as the majority opinion and Judge Moore's opinion as the concurring opinion.

[3] The majority characterizes the question in this case as turning on the breaking of covalent bonds linking the BRCA genes to the rest of the DNA in chromosomes 13 and 17, but its analysis appears to place patentable weight on the breaking of other chemical bonds, such as the hydrogen bonds that are broken when separating DNA from histones or—in an example unrelated to this case—the ionic bonds that are broken when lithium is derived from a salt. It is difficult to see why differences between types of chemical bonds should matter for patentability purposes, and I see little support for such a distinction in the governing precedents.

1, 12 (1931) (cleaning a shell by acid and then grinding off a layer with an emery wheel did not convert it into a different product). Nor should it make a difference for purposes of patentability if the portion of a wild plant that is collected for purposes of later regeneration is separated from the original plant by chemical means or by scissors.

Although the majority insists that the changes in the DNA molecule that occur as part of the process of isolation render the gene claims patentable, the majority does not appear to take a similar position with respect to chemical elements. The government as amicus curiae argues that patenting the BRCA genes would be like patenting the element lithium. Isolated lithium does not occur naturally because it reacts with air and water and thus is found in nature only as part of a chemical compound, ionically bound to other elements. Robert E. Krebs, *The History and Use of Our Earth's Chemical Elements* 48 (2d ed. 2006). Once isolated, lithium has many industrial applications, and in order to isolate lithium, it is necessary to break ionic bonds in the lithium compounds that are found in nature. But the majority acknowledges that elemental lithium (like other elements) would not be patentable subject matter because it "is the same element whether it is in the earth or isolated."

The principles underlying that analysis apply to genetic material as well. In order to isolate the BRCA gene, it is necessary to break chemical bonds that hold the gene in its place in the body, but the genetic coding sequence that is the subject of each of the BRCA gene claims remains the same whether the gene is in the body or isolated. The majority, however, does not agree that the cases are analogous, and indeed appears to have adopted the following rule: Isolated atoms are not patent eligible, but isolated molecules are.

Apart from the arbitrariness of such a rule, if we are to apply the conventional nomenclature of any field to determine whether Myriad's isolated DNA claims are "new," it would seem to make more sense to look to genetics, which provides the language of the claims, than to chemistry. Aside from Myriad's cDNA claims, its composition claims are not defined by any particular chemical formula. For example, claim 1 of the '282 patent covers all isolated DNAs coding for the BRCA1 protein, with the protein being defined by the amino acid sequence encoded by the naturally occurring BRCA1 gene. From a molecular perspective, that claim covers a truly immense range of substances from the cDNA that is 5,914 nucleotides long to the isolated gene that contains more than 120,000 nucleotides. And the patent does not define the upper end of that range because the patent does not identify a unique nucleotide sequence for the 120,000-nucleotide-long isolated BRCA1 gene. Instead, the patent contains a sequence that is just 24,000 nucleotides long with numerous gaps denoted "vvvvvvvvvvvvvv." '282 patent, fig. 10. An almost incalculably large number of new molecules could be created by filling in those gaps with almost any nucleotide sequence, and all of those molecules would fall within the scope of claim 1. Included in that set are many important molecular variations to the BRCA1 gene that Myriad had not yet discovered and could not have chemically described. Yet those molecules would share only one unifying characteristic: each codes for the same protein as the naturally occurring BRCA1 gene.

From a genetic perspective, that claim covers one "composition of matter"—the BRCA1 gene. The isolated BRCA genes are identical to the BRCA genes found on chromosomes 13 and 17. They have the same sequence, they code for the same proteins, and they represent the same units of heredity. During the transcription phase of protein synthesis, the BRCA genes are separated from chromosomal proteins. The transcription process then proceeds from a starting point called the promoter to a stopping point often called the terminator. James D. Watson et al., *Molecular Biology of the Gene* 382, 394-96 (6th ed. 2008). The only difference between the naturally occurring BRCA genes during transcription and the claimed isolated DNA is that the claimed genes have been isolated according to nature's predefined boundaries, i.e., at points that preserve the ability of the gene to express the protein for which it is coded.

In that respect, extracting a gene is akin to snapping a leaf from a tree. Like a gene, a leaf has a natural starting and stopping point. It buds during spring from the same place that it breaks off and falls during autumn. Yet prematurely plucking the leaf would not turn it into a human-made invention. *See Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282, 1295 (Fed. Cir. 2010) (Dyk, J., concurring in part and dissenting in part). That would remain true if there were minor differences between the plucked leaf and the fallen autumn leaf, unless those differences imparted "markedly different characteristics" to the plucked leaf. *Chakrabarty*, 447 U.S. at 310.

Both the majority and the concurring opinions attach significant weight to the fact that the claimed coding portions of the native BRCA genes are part of a much larger molecule and that the isolated BRCA genes, being smaller molecules extracted from the larger one, are therefore man-made inventions. But to argue that the isolated BRCA gene is patentable because in its native environment it is part of a much larger structure is no more persuasive than arguing that although an atom may not be patentable, a subatomic particle is patentable because it was previously part of a larger structure, or that while a tree is not patentable, a limb of the tree becomes a patentable invention when it is removed from the tree.

Of course, it is an oversimplification to say that something that can be characterized as "isolated" or "extracted" from its natural setting always remains a natural product and is not patentable. One could say, for example, that a baseball bat is "extracted" or "isolated" from an ash tree, but in that case the process of "extracting" the baseball bat necessarily changes the nature, form, and use of the ash tree and thus results in a manmade manufacture, not a naturally occurring product. In that setting, man has defined the parts that are to be retained and the parts that are to be discarded. The result of the process of selection is a product with a function that is entirely different from that of the raw material from which it was obtained. In the case of the BRCA genes, by contrast, nature has defined the genes as independent entities by virtue of their capacity for protein synthesis and, ultimately, trait inheritance. Biochemists extract the target genes along lines defined by nature so as to preserve the structure and function that the gene possessed in its natural environment. In such a case, the extraction of a product in a manner that retains the character and function of the product as found in nature does not result in the creation of a human invention.[4]

That principle was captured by the Supreme Court's statement in *Chakrabarty* that the invention in that case was not to "a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter 'having a distinctive name, character [and] use.'" 447 U.S. at 309-10.

Cases involving the "purification" of a natural substance employ similar analysis. Our predecessor court recognized that merely purifying a naturally occurring substance does not render the substance patentable unless it results in a marked change in functionality. *In re Merz*, 97 F.2d 599, 601 (CCPA 1938) (holding that there was no right to a patent on a purer version of ultramarine, but recognizing that if a claimed article is "of such purity that it differs not only in degree but in kind it may be patentable"); *see also In re King*, 107 F.2d 618, 620 (CCPA 1939) (same, for purified vitamin C); *In re Marden*, 47 F.2d 958, 959 (CCPA 1931) (same, for purified vanadium); *Gen. Elec. Co. v. DeForest Radio Co.*, 28 F.2d 641,

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[4] By analogy, extracting a slab of marble from the earth does not give rise to protectable intellectual property rights, but "extracting" a piece of sculpture from that slab of marble does. In the case of the BRCA gene claims, what Myriad has claimed is more akin to the slab of marble found in the earth than to the sculpture carved from it after its extraction.

643 (3d Cir. 1928) (same, for purified tungsten). On the other hand, the purified natural substance is patentable if the "purification" results in a product with such distinct characteristics that it becomes "for every practical purpose a new thing commercially and therapeutically." *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95, 103 (C.C.S.D.N.Y. 1911); *see also Merck & Co. v. Olin Mathieson Chem. Corp.*, 253 F.2d 156, 161-64 (4th Cir. 1958) (holding that a purified composition of vitamin B-12 was patentable because the purification process resulted in a product that was therapeutically effective, whereas the natural form was not).

In sum, the test employed by the Supreme Court in *Chakrabarty* requires us to focus on two things: (1) the similarity in structure between what is claimed and what is found in nature and (2) the similarity in utility between what is claimed and what is found in nature. What is claimed in the BRCA genes is the genetic coding material, and that material is the same, structurally and functionally, in both the native gene and the isolated form of the gene.

The structural differences between the claimed "isolated" genes and the corresponding portion of the native genes are irrelevant to the claim limitations, to the functioning of the genes, and to their utility in their isolated form. The use to which the genetic material can be put, i.e., determining its sequence in a clinical setting, is not a new use; it is only a consequence of possession. In order to sequence an isolated gene, each gene must function in the same manner in the laboratory as it does in the human body. Indeed, that identity of function in the isolated gene is the key to its value. Moreover, as Judge Moore's concurring opinion explains, Myriad has failed to credibly identify new uses for the isolated BRCA genes as probes or primers. The naturally occurring genetic material thus has not been altered in a way that would matter under the standard set forth in *Chakrabarty*. For that reason, the isolation of the naturally occurring genetic material does not make the claims to the isolated BRCA genes patent-eligible.

II.

As noted, in addition to the BRCA gene claims discussed above, the claims at issue in this appeal include four claims to BRCA cDNA and two claims to portions of the BRCA genes and cDNA as small as 15 nucleotides long.

I agree with the court that the claims to BRCA cDNA are eligible for patenting. The cDNA cannot be isolated from nature, but instead must be created in the laboratory.[5] Although that process occurs with natural machinery, the end product is a human-made invention with distinct structure because the introns that are found in the native gene are removed from the cDNA segment. Additionally, the cDNA has a utility not present in the naturally occurring BRCA DNA and mRNA because cDNA can be attached to a promoter and inserted into a non-human cell to drive protein expression.

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[5] The appellees argue that the BRCA1 cDNA can be isolated from nature, and they refer to a BRCA1 pseudogene called BRCA1P1 that is found in the human genome. However, the appellees have failed to demonstrate that the pseudogene consists of the same sequence as the BRCA1 cDNA.

However, I disagree with the court as to the two claims to short segments of DNA having at least 15 nucleotides. Claim 6 of the '282 patent covers any sequence of the BRCA1 cDNA that is at least 15 nucleotides long. That claim encompasses each BRCA1 exon, even though each exon is naturally defined by transcription. Moreover, because small sequences of DNA are repeated throughout the three billion nucleotides of the human genome, the claim covers portions of the cDNA of more than 4% of human genes. It also covers portions of the DNA of nearly all human genes. Accordingly, efforts to sequence almost any gene could infringe claim 6 even though Myriad's specification has contributed nothing to human understanding of other genes.

Myriad could easily have claimed more narrowly to achieve the utility it attaches to segments of cDNA. It contends that those segments can be used as probes and primers. DNA probes must be chemically altered or "tagged" before they can be so used, and Myriad could have claimed the tagged segments to achieve probe functionality. A claim to tagged segments would not encompass the BRCA1 exons. As to primer functionality, many of the cDNA segments will not work. Some will be too long. Some will be too short. Some will be palindromic and fold in on themselves. Myriad could have identified a subset of the segments that work as primers, and such a claim could be patentable if it were limited to species with "markedly different characteristics from any found in nature and . . . having the potential for significant utility." *Chakrabarty*, 447 U.S. at 310.

The problem with claim 6 is that it is so broad that it includes products of nature (the BRCA1 exons) and portions of other genes; its validity is not salvaged because it includes some species that are not natural. Accordingly, I would hold claim 6 unpatentable.

Myriad's last claim, claim 5 of the '282 patent, is breathtakingly broad. That claim covers any segment of the DNA defined by claim 1, provided that the segment is at least 15 nucleotides long. Claim 1, in turn, covers any isolated DNA that codes for the BRCA1 polypeptide. Thus, claim 5 would cover not only the isolated BRCA1 gene in each of its untold molecular variations, but also any subsequence of those molecules, including portions that fall in the undefined range of those molecules denoted "vvvvvvvvvvvvv." Claim 5 would therefore be unpatentable for the same reasons as claim 1 and claim 6.

Of course, in light of its breadth, claim 5 of the '282 patent is likely to be invalid on other grounds, and thus a ruling as to patent-eligibility with respect to that claim may be superfluous. Nonetheless, it is important to consider the effects of such broad patent claims on the biotechnology industry. While Myriad has emphasized the biotechnology industry's need of patent protection to encourage and reward research in this difficult and important field, there is another side to the coin. Broad claims to genetic material present a significant obstacle to the next generation of innovation in genetic medicine—multiplex tests and whole-genome sequencing. New technologies are being developed to sequence many genes or even an entire human genome rapidly, but firms developing those technologies are encountering a thicket of patents. Secretary's Advisory Comm. on Genetics, Health, and Society, Dep't of Health & Human Servs., *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests* 49-62 (2010). In order to sequence an entire genome, a firm would have to license thousands of patents from many different licensors. *See id.* at 50-51. Even if many of those patents include claims that are invalid for anticipation or obviousness, the costs involved in determining the scope of all of those patents could be prohibitive. *See id.* at 51-52; Rebecca S. Eisenberg, *Noncompliance, Nonenforcement, Nonproblem? Rethinking the Anticommons in Biomedical Research*, 45 Hou. L. Rev. 1059, 1076-1080 (2008) (concluding that existing studies "have focused relatively little attention on downstream product development" and that interviews accompanying those studies suggest that, though smaller than initially feared, the costs associated with the patent thicket are "quite real in the calculations of product-developing firms"). In light of these considerations, this may well be one of those instances in which "*too much* patent protection can impede rather than 'promote the Progress of Science and useful Arts.'" *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 126 (2006) (Breyer, J., dissenting from dismissal of writ as improvidently granted).

My colleagues assign significant weight to the fact that since 2001 the PTO has had guidelines in place that have allowed patents on entire human genes. They conclude that those guidelines, and the PTO's earlier practice, are entitled to deference from this court as to the question whether patents to isolated human genes constitute patent-eligible subject matter. I think the PTO's practice and guidelines are not entitled to significant weight, for several reasons.

First, as we have recognized, the PTO lacks substantive rulemaking authority as to issues such as patentability. *Animal Legal Def. Fund v. Quigg*, 932 F.2d 920, 930 (Fed. Cir. 1991). In areas of patent scope, we owe deference only commensurate with the "the thoroughness of its consideration and the validity of its reasoning." *Merck & Co. v. Kessler*, 80 F.3d 1543, 1550 (Fed. Cir. 1996). The comments that the PTO issued at the time of its 2001 guidelines in response to suggestions that isolated human genes were not patentable are, frankly, perfunctory. *See* John M. Conley & Roberte Makowski, *Back to the Future: Rethinking the Product of Nature Doctrine as a Barrier to Biotechnology Patents*, 85 J. Pat. & Trademark Off. Soc'y 301 (2003). Because those comments, at least on their face, do not reflect thorough consideration and study of the issue, I do not regard them as worthy of much weight in the analysis of this complex question.

Second, whatever force the PTO's views on the issue of patent eligibility may have had in the past has, at the very least, been substantially undermined by the position the government has taken in this case. The Department of Justice filed a brief on behalf of the United States in this court taking the position that Myriad's gene claims (other than the cDNA claims) are not patent-eligible. Although the PTO did not "sign" the brief and we are left to guess about the status of any possible continuing inter-agency disagreements about the issue, the Department of Justice speaks for the Executive Branch, and the PTO is part of the Executive

Branch, so it is fair to assume that the Executive Branch has modified its position from the one taken by the PTO in its 2001 guidelines and, informally, before that.

Finally, prior to the Supreme Court's decision in *Chakrabarty*, the PTO had determined that microorganisms were not subject to patenting, but the Supreme Court gave no indication that it regarded that view as entitled to deference. Moreover, the Court gave short shrift to the Commissioner's contention (which was made the lead argument in its brief) that the patentability of life-forms was an issue that should be left to Congress. Citing *Marbury v. Madison*, 5 U.S. (1 Cranch) 137 (1803), the Court explained that "Congress has performed its constitutional role in defining patentable subject matter in § 101; we perform ours in construing the language Congress has employed." *Chakrabarty*, 477 U.S. at 315. We have the same responsibility and should not shy away from deciding the issues of law that the parties have brought to us. Although my colleagues believe our analysis of the legal question in this case should be influenced by purported expectations of the inventing community based on the PTO's past practice of issuing patents on human genes, that is in effect to give the PTO lawmaking authority that Congress has not accorded it.[6] There is no collective right of adverse possession

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[6] Because the asserted reliance interest is based on PTO practice and not on prior judicial decisions, this case is not analogous to *Warner Jenkinson Co. v. Hilton Davis Chemical Co.*, 520 U.S. 17 (1997), or *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002), where the expectations of the inventing community were based on longstanding Supreme Court precedent.

to intellectual property, and we should not create such a right. Our role is to interpret the law that Congress has written in accordance with the governing precedents. I would do so and would affirm the district court's rulings as to the BRCA gene and BRCA gene segment claims.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

ASSOCIATION FOR MOLECULAR PATHOLOGY, ET. AL., *Plaintiffs,*	09 Civ. 4515 AMENDED OPINION

--against--

UNITED STATES PATENT AND
TRADEMARK OFFICE, ET AL.,
Defendants.

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Sweet, D.J.

Plaintiffs Association for Molecular Pathology, et al. (collectively "Plaintiffs") have moved for summary judgment pursuant to Rule 56, Fed. R. *Civ.* P., to declare invalid fifteen claims (the "claims-in-suit") contained in seven patents (the "patents-in-suit") relating to the human *BRCA1* and *BRCA2* genes (Breast Cancer Susceptibility Genes 1 and 2) (collectively, *"BRCA1/2")* under each of (1) the Patent Act, 35 U.S.C. § 101 (1952), (2) Article I, Section 8, Clause 8 of the United States Constitution, and (3) the First and Fourteenth Amendments of the Constitution because the patent claims cover products of nature, laws of nature and/or natural phenomena, and abstract ideas or basic human knowledge or thought. The defendant United States Patent and Trademark *Office* ("USPTO") issued the patents-in-suit which are held by defendants Myriad Genetics and the University of Utah Research Foundation ("UURF") (collectively "Myriad" or the "Myriad Defendants"). Myriad has cross-moved under Rule 56, Fed. R. Civ. P., for summary judgment dismissing Plaintiffs' complaint, and the USPTO has cross-moved under Rule 12(c), Fed. R. Civ. P., for judgment on the pleadings. Based upon the findings and conclusions set forth below, the motion of Plaintiffs to declare the claims-in-suit invalid is granted, the cross-motion of Myriad is denied, and the motion of the USPTO is granted.

As discussed infra in greater detail, the challenged patent claims are directed to (1) isolated DNA containing all or portions of the *BRCA1* and *BRCA2* gene sequence and (2) methods for "comparing" or "analyzing" *BRCA1* and *BRCA2* gene sequences to identify the presence of mutations correlating with a predisposition to breast or ovarian cancer. Plaintiffs' challenge to the validity of these Claims, and the arguments presented by the parties and amici, have presented a unique and challenging question:

> Are isolated human genes and the comparison of their sequences patentable?

Two complicated areas of science and law are involved: molecular biology and patent law. The task is to seek the governing principles in each and to determine the essential elements of the claimed biological compositions and processes and their relationship to the laws of nature. The resolution of the issues presented to this Court deeply concerns breast cancer patients, medical professionals, researchers, caregivers, advocacy groups, existing gene patent holders and their investors, and those seeking to advance public health.

The claims-in-suit directed to "isolated DNA" containing human *BRCA1/2* gene sequences reflect the USPTO's practice of granting patents on DNA sequences so long as those sequences are claimed in the form of "isolated DNA." This practice is premised on the view that DNA should be treated no differently from any other chemical compound, and that its purification from the body, using well-known techniques, renders it patentable by transforming it into something distinctly different in character. Many, however, including scientists in the fields of molecular biology and genomics, have considered this practice a "lawyer's trick"[1] that circumvents the prohibitions on the direct patenting of the DNA in our bodies but which, in practice, reaches the same result. The resolution of these motions is based upon long recognized principles of molecular biology and genetics: DNA represents the physical embodiment of biological information, distinct in its essential characteristics from any other chemical found in nature. It is concluded that DNA's existence in an "isolated" form alters neither this fundamental quality of DNA as it exists in the body nor the information it encodes. Therefore, the patents at issue directed to "isolated DNA" containing sequences found in nature are unsustainable as a matter of law and are deemed unpatentable subject matter under 35 U.S.C. § 101.

Similarly, because the claimed comparisons of DNA sequences are abstract mental processes, they also constitute unpatentable subject matter under § 101.

The facts relating to molecular biology are fundamental to the patents at issue and to the conclusions reached. Consequently, in the findings which follow, the discussion of molecular biology precedes the facts concerning the development, application, and description of the patents. Following those facts are the conclusions which compel the partial grant of summary judgment to the Plaintiffs, the denial of Myriad's cross-motion, and the grant of the USPTO's motion for judgment on the pleadings.

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[1] See, e.g., John M. Conley & Roberte Markowski, Back to the Future: Rethinking the Product of Nature Doctrine as a Barrier to Biotechnology Patents, 65 J. Pat. & Trademark Off. Soc'y 301, 3C5 (2003).

I. PRIOR PROCEEDINGS

The complaint in this action was filed on May 12, 2009, alleging violations of 35 U.S.C. § 101; Article I, Section 8, Clause 8 of the United States Constitution; and the First and Fourteenth Amendments to the Constitution.

Defendants moved to dismiss the complaint which motion was denied by the opinion of November 1, 2009. See Assoc. for Molecular Pathology v. U.S. Patent and Trademark Office, 669 F. Supp. 2d 365 (S.D.N.Y. 2009). Plaintiffs were found to have the necessary standing to assert their declaratory judgment claims against the Myriad Defendants and the USPTO, and specific personal jurisdiction was found to exist over the Directors of the UURF by virtue of acts performed in their official capacity that were directed to the state of New York. It was also determined that this Court possessed the necessary subject matter jurisdiction to hear Plaintiffs' constitutional claims against the USPTO and that the complaint satisfied the pleading requirements set forth in Ashcroft v. Iqbal, 129 S. Ct. 1937 (2009).

Plaintiffs' motion for summary judgment and the cross-motions for summary judgment and judgment on the pleadings were heard and marked fully submitted on February 4, 2010.

II. THE PARTIES AND AMICI

Plaintiff Association for Molecular Pathology ("AMP") is a not-for-profit scientific society dedicated to the advancement, practice, and science of clinical molecular laboratory medicine and translational research based on the applications of genomics and proteomics. AMP members participate in basic and translational research aimed at broadening the understanding of gene/protein structure and function, disease processes, and molecular diagnostics, and provide clinical medical services for patients, including diagnosis of breast cancer. Sobel Decl. ¶¶ 2, 4-5.[2]

Plaintiff the American College of Medical Genetics ("ACMG") is a private, non-profit voluntary organization of clinical and laboratory geneticists. The Fellows of the ACMG are doctoral level medical geneticists and other physicians involved in the practice of medical genetics. With more than 1300 members, the ACMG's mission is to improve health through the practice of medical genetics. In order to fulfill this mission, the ACMG strives to define and promote excellence in medical genetics practice and the integration of translational research into practice; promote and provide medical genetics education; increase access to medical genetics services and integrate genetics into patient care; and advocate for and represent providers of medical genetics services and their patients. Watson Decl. ¶¶ 2, 4-5.

Founded in 1922, plaintiff the American Society for Clinical Pathology ("ASCP") is the largest and oldest organization representing the medical specialty of pathology and laboratory medicine. ASCP is a not-for-profit entity organized for scientific and educational purposes and dedicated to patient safety, public health, and the practice of pathology and laboratory medicine and has 130,000 members working as pathologists and laboratory professionals. ASCP members design and interpret the tests that detect disease, predict outcome, and determine the appropriate therapy for the patient. The ASCP is recognized for its excellence in continuing professional education, certification of laboratory professionals, and advocacy. Ball Decl. ¶¶ 2, 5.

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[2] For purposes of this opinion, references to the parties' declarations will be in the format [Declarant name] Decl. ¶ [paragraph number].

Plaintiff the College of American Pathologists ("CAP") is a national medical society representing more than 17,000 pathologists who practice anatomic pathology and laboratory medicine in laboratories worldwide. The College's Commission on Laboratory Accreditation is responsible for accrediting more than 6,000 laboratories domestically and abroad, and approximately 23,000 laboratories are enrolled in CAP's proficiency testing programs. It is the world's largest association composed exclusively of board-certified pathologists and pathologists in training worldwide and is widely considered the leader in laboratory quality assurance. CAP is an advocate for high quality and cost-effective medical care. Scott Decl. ¶¶ 2, 4-5.

Plaintiff Haig Kazazian, M.D. ("Dr. Kazazian"), is the Seymour Gray Professor of Molecular Medicine in Genetics in the Department of Genetics at the University of Pennsylvania School of Medicine. He is a human genetics researcher and the previous chair of the Department. Dr. Kazazian and plaintiff Arupa Ganguly, Ph.D. ("Dr. Ganguly"), designed tests to screen the *BRCA1* and *BRCA2* genes in their lab and provided screening to approximately 500 women per year starting in 1996. Drs. Kazazian and Ganguly ceased their *BRCA1/2* testing in response to cease-and-desist letters from Myriad relating to the patents-in-suit. Kazazian Decl. ¶¶ 1-5.

Plaintiff Dr. Ganguly is an Associate Professor in the Department of Genetics at the Hospital of the University of Pennsylvania. Dr. Ganguly's work previously included *BRCA1/2* screening for both research and clinical purposes. She ceased *BRCA1/2* screening following her receipt of cease-and-desist letters from Myriad accusing her lab of violating the patents-in-suit. Ganguly Decl. ¶¶ 1, 3-5.

Plaintiff Wendy Chung, M.D., Ph.D. ("Dr. Chung"), is an Associate Professor of Pediatrics and the Herbert Irving Professor of Pediatrics and Medicine in the Division of Molecular Genetics at Columbia University. Dr. Chung is a human geneticist whose current research includes research on the *BRCA1* and *BRCA2* genes. Because of the patents-in-suit, Dr. Chung currently cannot tell research subjects in her studies the results of their *BRCA1/2* tests and cannot offer clinical *BRCA1/2* testing services. Chung Decl. ¶¶ 1-9, 13, 16.

Plaintiff Harry Ostrer, M.D. ("Dr. Ostrer"), is a Professor of Pediatrics, Pathology and Medicine and Director of the Human Genetics Program in the Department of Pediatrics at New York University School of Medicine. Dr. Ostrer's work has focused on understanding the genetic basis of development and disease, including disorders of sexual differentiation and genetic susceptibility to breast and prostate cancer and malignant melanoma. Dr. Ostrer is actively engaged in identifying genes that convey risk of breast cancer and that may mitigate the effects of mutations in the *BRCA1* and *BRCA2* genes. Dr. Ostrer is also the Director of the Molecular Genetics Laboratory of NYU Medical Center, one of the largest academic genetic testing laboratories in the United States. Because of the patents-in-suit, Dr. Ostrer currently cannot tell research subjects in his studies the results of their *BRCA1/2* tests and cannot offer clinical *BRCA1/2* testing services. Ostrer ¶¶ 1-4.

Plaintiff David Ledbetter, Ph.D. ("Dr. Ledbetter"), is a Professor of Human Genetics and Director of the Division of Medical Genetics at the Emory University School of Medicine. Research in his laboratory focuses on the molecular characterization of human developmental disorders. Dr. Ledbetter directs the Emory Genetics Laboratory which provides testing services for individuals with or at risk for genetic diseases. Because of the patents-in-suit, Dr. Ledbetter cannot offer comprehensive *BRCA1/2* genetic testing to patients. Ledbetter Decl. ¶¶ 1-8, 16.

Plaintiff Stephen T. Warren, Ph.D. ("Dr. Warren"), is the William Patterson Timmie Professor of Human Genetics, Chairman of the Department of Human Genetics, and Professor of Biochemistry and Professor of Pediatrics at Emory University. He is a past President of the American Society of Human Genetics. Dr. Warren supervises genetic research at Emory and is responsible for the laboratories at the Emory Genetics Laboratory. These laboratories would offer *BRCA1/2* genetic testing but for the patents-in-suit. Ledbetter Decl. ¶¶ 1, 16.

Plaintiff Ellen Matloff, M.S. ("Ms. Matloff"), is Director of the Yale Cancer Genetic Counseling Program. Ms. Matloff advises women on the desirability of obtaining an analysis of their genes to determine if the women have the genetic mutations that correlate with an increased risk of breast and/or ovarian cancer. If she determines that such an analysis is warranted and the individual woman concurs, Ms. Matloff arranges for the analysis and then advises the woman of the significance of the results. Ms. Matloff would like to have the option to send patient samples to laboratories other than Myriad Genetics for *BRCA1/2* sequencing. Matloff Decl. ¶¶ 1-4, 11.

Plaintiff Elsa W. Reich, M.S. ("Ms. Reich"), is a Professor in the Department of Pediatrics at New York University. She is a genetic counselor. She helps women decide whether to be tested for mutations in the *BRC1* and *BRCA2* genes. If they need testing, she sends samples to Myriad and explains the results for the women. Ms. Reich would like to have the option to send patient samples to laboratories other than Myriad for *BRCA1/2* sequencing. Reich Decl. ¶¶ 1-3, 8.

Plaintiff Breast Cancer Action ("BCA") is a national organization of approximately 30,000 members based in San Francisco, California. BCA is dedicated to representing the voices of people affected by breast cancer in order to inspire and compel the changes necessary to end the breast cancer epidemic. Its members include breast cancer survivors, family members of people diagnosed with breast cancer and other people affected by or concerned about breast cancer. BCA advocates for policy changes directed at achieving prevention, finding better treatments, and reducing the incidence of breast cancer, provides information about breast cancer to anyone who needs it via newsletters, web sites, email and a toll-free number, and organizes people to get involved in advocacy to advance its policy goals. Brenner Decl. ¶¶ 1-3.

Plaintiff Boston Women's Health Book Collective, doing business as Our Bodies Ourselves ("OBOS"), is a nonprofit, public interest women's health education, advocacy, and consulting organization. OBOS provides information about health, sexuality and reproduction from a feminist and consumer perspective. OBOS advocates for women's health and provides information to members of the public about genetic analysis. Norsigian Decl. ¶¶ 1-4.

Plaintiff Lisbeth Ceriani ("Ms. Ceriani") is a 43-year-old single mother who was diagnosed with cancer in both breasts in May 2008. Ms. Ceriani is insured through MassHealth, a Medicaid insurance program for low-income people. Her oncologist and genetic counselor recommended that she obtain *BRCA1* and *BRCA2* genetic testing because she may need to consider further surgery in order to reduce her risk of ovarian cancer. However, Myriad will not accept the MassHealth coverage, and Ms. Ceriani is unable to pay the full cost out-of-pocket. Ceriani Decl. ¶¶ 1-6.

Plaintiff Runi Limary ("Ms. Limary") is a 32-year-old Asian-American woman who was diagnosed with aggressive breast cancer in 2005. Ms. Limary obtained *BRCA1/2* testing through Myriad and received the following result: "genetic variant of uncertain significance." Because of Myriad's patents, she is unable to pursue alternative testing options. Limary Decl. ¶¶ 1-5.

Plaintiff Genae Girard ("Ms. Girard") is a 39-year-old woman who was diagnosed with breast cancer in 2006. Shortly after her diagnosis, she obtained *BRCA1/2* genetic testing from Myriad and tested positive for a deleterious mutation on the *BRCA2* gene. She sought a second opinion of that test result but learned that Myriad is the only laboratory in the country that can provide full *BRCA1/2* sequencing. Girard Decl. ¶¶ 1-6.

Plaintiff Patrice Fortune ("Ms. Fortune") is a 48-year-old woman who was diagnosed with breast cancer in February 2009. Ms. Fortune is insured through Medi-Cal. Her oncologist and genetic counselor recommended that she obtain *BRCA1/2* genetic testing, including the supplemental testing that is offered by Myriad separate from its standard test, but told her that Myriad would not accept her insurance. Ms. Fortune is unable to pay the full cost out-of-pocket. Fortune Decl. ¶¶ 1-5.

Plaintiff Vicky Thomason ("Ms. Thomason") is a 52-year-old woman who was diagnosed with ovarian cancer in 2006. She obtained *BRCA1/2* genetic testing from Myriad in 2007 and was found to be negative for mutations covered by that test. Her genetic counselor advised her about additional *BRCA1/2* genetic testing offered by Myriad that looks for other large genetic rearrangements that are not included in Myriad's standard full sequencing test, but informed her that her insurance would not cover the full cost of that test. Ms. Thomason is unable to afford the extra cost. Thomason Decl. ¶¶ 1-8.

Plaintiff Kathleen Raker ("Ms. Raker") is a 41-year-old woman whose mother and maternal grandmother died from breast cancer. She obtained *BRCA1/2* genetic testing from Myriad in 2007 and was found to be negative for mutations covered by that test. Her genetic counselor advised her about additional *BRCA1/2* genetic testing offered by Myriad that looks for other large DNA rearrangements that are not included in Myriad's standard full sequencing test, but informed her that it was unclear whether her insurance would cover the full cost of that test. Ms. Raker is unable to afford the extra cost. Raker Decl. ¶¶ 1-9.

Defendant USPTO is an agency of the Commerce Department of the United States with its principal office in Alexandria, Virginia. USPTO Answer ¶ 27.

Defendant Myriad is a for-profit corporation incorporated in Delaware with its principal place of business in Salt Lake City, Utah. Myriad is the former co-owner of several of the patents-in-suit and the current exclusive licensee of the patents-in-suit. Myriad is the sole provider of full sequencing of *BRCA1* and *BRCA2* genes in the United States on a commercial basis. Myriad Answer ¶ 28.

The University of Utah Research Foundation, whose directors are named as defendants in their official capacity, is an owner or part-owner of each of the patents-in-suit. Myriad Answer ¶ 29.

Amici curiae American Medical Association American Society of Human Genetics, American College of Obstetricians and Gynecologists, American College of Embryology, and The Medical Society of the State of New York are non-profit organizations representing physicians and medical students throughout the United States, including New York; professionals in the field of human genetics, including researchers, clinicians, academicians, ethicists, genetic counselors and nurses whose work involve genetic testing; women's health care professionals; and embryologists. These amici contend that the patents-in-suit are directed to unpatentable natural phenomena in violation of Article I, Section 8, Clause B of the Constitution, and 35 U.S.C. § 101, are unnecessary to promote innovation in genetic research, and violate medical and scientific ethics.

Amici curiae March of Dimes Foundation, Canavan Foundation, Claire Altman Heine Foundation, Breast Cancer Coalition, Massachusetts Breast Cancer Coalition, National Organization for Rare Disorders, and National Tay-Sachs & Allied Diseases Association are non-profit organizations dedicated to advancing the treatment of a variety of genetic diseases, including breast cancer, Tay-Sachs, Spinal Muscular Dystrophy, Canavan disease, and other rare genetic disorders. These amici contend that Myriad's patents represent patents on natural phenomena and laws of nature, thereby restricting future research and scientific progress.

Amici curiae National Women's Health Network, Asian Communities for Reproductive Justice, Center for Genetics and Society, Generations

Ahead, and Pro-Choice Alliance for Responsible Research are non-profit organizations seeking to improve the health of women; promote reproductive justice; encourage responsible use and governance of genetic, reproductive and biomedical technologies; promote policies on genetic technologies that protect human rights; promote accountability, safety, and social justice in biomedical research from a women's rights perspective. These amici contend that isolated DNA constitutes an unpatentable product of nature whose patenting harms women by stifling innovation and interfering with patient access to medical testing and treatment. These amici also contend that human genes and the information contained therein constitute part of the common heritage of humanity, and patenting human gene sequences is contrary to both international law and treatises as well as the public trust doctrine.

Amici curiae The International Center for Technology Assessment, Indigenous People Council on Biocolonialism, Greenpeace, Inc., and Council for Responsible Genetics are non-profit organizations dedicated to assisting the public and policy makers in understanding how technology affects society, protecting the cultural heritage and genetic materials of indigenous peoples; addressing global environmental problems; and protecting the public interest and fostering public debate about the social, ethical, and environmental implications of genetic technologies. These amici contend that the patents-in-suit claim unpatentable products of nature and that gene patents have significant negative consequences, including privatization of genetic heritage in violation of fundamental precepts of common heritage, public domain, and the public trust doctrine; creation of private rights of unknown scope and significance; facilitate the exploitation of indigenous peoples; and violation of patients' rights to informed consent.

Amicus curiae Biotechnology Industry Organization ("BIO") is the country's largest biotechnology trade association, representing over 1200 companies, academic institutions, and biotechnology centers in all 50 states. BIO members are involved in the research and development of biotechnological healthcare, agricultural, environmental, and industrial products. BIO member companies range from start-up businesses and university spin-offs to large Fortune 500 corporations. BIO contends that patents directed to isolated DNA fall within the categories of patent-eligible subject matter because they differ "in kind" from naturally-occurring DNA. The BIO also contends that patents such as the ones in dispute here provide incentives for investment in biotechnology that promotes the advancement of science.

Amicus curiae Boston Patent Law Association ("BPLA") is a non-profit association of attorneys and other intellectual property professionals. BPLA's members serve a broad range of clients who rely on the patent system, including independent investors, corporations, investors, and non-profit and academic institutions, such as universities and research hospitals. BPLA contends that patents, including patents on gene-related inventions, promote innovation by protecting investments in the innovation process. It further contends that the patents-in- suit satisfy the requirements of 35 U.S.C. § 101 as well as the Constitution.

Amicus curiae Genetic Alliance ("GA") is a not-for-profit, tax-exempt health advocacy organization founded in 1986 (as the Alliance for Genetic Support Groups). It brings together diverse stakeholders that create novel partnerships in advocacy. By integrating individual, family, and community perspectives to improve health systems, Genetic Alliance seeks to revolutionize access to information to enable translation of research into services and individualized decision-making. GA contends that the wholesale abolition of patents on isolated DNA molecules and isolated purified natural substances is legally untenable and undesirable as public policy, because it would diminish the promise of genetic research for patients and negatively affect other areas of medicine.

Amicus curiae Rosetta Genomics, Inc. is a wholly owned subsidiary of amicus curiae Rosetta Genomics, Ltd., a molecular diagnostics company that provides diagnostic tests for cancer and which owns several patents claiming isolated nucleic acid sequences. Amicus curiae George Mason University ("George Mason") is a public university located in Virginia. Research conducted at George Mason has been incorporated into patent applications covering cancer diagnostics. These amici contend that the question of patentability of human gene sequences is appropriately left to Congress; that the patents-in-suit promote, rather than hinder innovation; and that the challenged patents are lawful under 3S U.S.C. § 101 and the Constitution.

Amicus curiae BayBio is an independent, nonprofit 501(c) (6) trade association serving the life sciences industry in Northern California, and represents more than 330 companies involved in the research and development of treatments, cures, and diagnostics. Amicus curiae Celera Corporation is a manufacturer of diagnostic products that include gene-based products used in genetic testing. Amicus curiae The Coalition for 21st Century Medicine represents some of the world's most innovative diagnostic technology companies, clinical laboratories, researchers, physicians, venture capitalists, and patient advocacy groups that share a common mission to develop advanced diagnostics that improve the quality of healthcare for patients. Amicus curiae Genomic Health, Inc., is a life sciences company committed to improving the quality of cancer treatment decisions through genomics-based clinical laboratory services and currently offers the Oncotype DX breast cancer assay, which predicts the likelihood of the recurrence of specific types of breast cancer and whether a patient will benefit from certain treatment strategies. Amicus curiae Qiagen, N.V. is a leading provider of innovative sample and assay technologies and products which are considered standard for use in molecular diagnostics, applied testing, and academic and pharmaceutical research and development. Amicus curiae Target Discovery, Inc. discovers, validates, and utilizes protein isoforms to improve clinical diagnosis and management of disease. Amicus curiae XDx, Inc., is a molecular diagnostics company focused on the discovery, development and commercialization of non-invasive gene expression testing in the areas of transplant medicine and autoimmunity through the use of modern genomics and bioinformatics technology. These amici contend that patent exclusivity is required for the development of personalized medicine and that the challenged patents satisfy the requirements of 35 U.S.C. § 101 and the Constitution. In addition, the amici contend that the harm alleged by Plaintiffs can be redressed through traditional judicial remedies and do not require a finding that isolated DNA constitutes unpatentable subject matter.

Amicus curiae Kenneth Chahine, Ph.D. ("Professor Chahine"), is a Visiting Professor of Law at S.J. Quinney College of Law at the University of Utah. Professor Chahine contends that the scope of the claims-in-suit are sufficiently limited to avoid claiming products of nature and that the claims directed to isolated DNA and diagnostic process satisfy the requirements of patentable subject matter under 35 U.S.C. § 101.

Amicus curiae Kevin E. Noonan, Ph.D. ("Dr. Noonan"), is a patent attorney with McDonnell Boehnen Hulbert & Berghoff LLP. Dr. Noonan contends that isolated human DNA constitutes patentable subject matter and that a ban on patenting isolated human DNA would negatively affect the development of human therapeutics, the development of personalized medicine, and the scientific research in general.

III. THE FACTS

The facts as set forth in this section are taken from the parties' respective statements and counterstatements pursuant to Local Civil Rule 56.1

and the affidavits submitted by the parties and amici and are not in dispute except where noted.

A. The Development of Genetics as a Field of Knowledge

The field of genetics the science of heredity and variation in living organisms - and the concept of units of heredity that could be transmitted from one generation to another originated in the 19th century from experiments with pea plants conducted by Gregor Mendel. Mendel showed that certain traits are passed on from parent to offspring as discrete entities and do not appear blended in the offspring. He hypothesized that it was the plant's genotype, or assortment of hereditary factors, that determined the plant's phenotype, or appearance. Mason Decl. ¶ 8. In 1909, this unit of inheritance was termed a "gene." Yet the gene remained an abstract concept until 1915, when it was shown that genes corresponded to physical spans of chromosomal material. Mason Decl. ¶ 9.

In 1944, scientists determined that the chemical compound known as deoxyribonucleic acid, or DNA,[3] served as the carrier for genetic information by demonstrating that DNA extracted from one strain of bacteria and transferred to another strain could transfer certain characteristics found in the first strain. Oswald Theodore Avery, et al., Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types: Induction of Transformation by a Desoxyribonucleic Acid Fraction Isolated from Pneumococcus Type III, 79 J. Exp. Med. 137- 158 (1944).

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[3] Scientists had learned to extract DNA from the body by removing it from the rest of the cellular material since as early as 1869. Ralf Dahm, Discovering DNA: Friedrich Miescher and the Early Years of Nucleic Acid Research, 122 Human Genetics 565-581, 567-68 (2008).

On April 25, 1953, James Watson and Francis Crick published their determination of the famous double-helix structure of DNA in the journal *Nature.* James D. Watson & Francis H.C. Crick, A Structure for Deoxyribose Nucleic Acid, 171 Nature 737-38 (1953). Dr. Crick subsequently contributed to the decryption of the genetic code and proposed "the central dogma" of molecular biology: (1) information is encoded in a segment of DNA, i.e., a gene; (2) transmitted through a molecule called RNA; and then (3) utilized to direct the creation of a protein, the building block of the body. Mason Decl. ¶ 10.

Our understanding of the DNA contained within our cells has since grown at an exponential rate and has included the landmark completion of the first full-length sequence of a human genome, containing 25,000 genes, as a result of the work performed by the Human Genome Project from 1990 to 2003. Sulston Decl. ¶¶ 11, 22. Access to the information encoded in our DNA has presented expansive new possibilities for future biomedical research and the development of novel diagnostic and therapeutic approaches. How this genomic information is best harnessed for the greater good presents difficult questions touching upon innovation policy, social policy, medical ethics, economic policy, and the ownership of what some view as our common heritage.

B. Molecular Biology and Gene Sequencing

An understanding of the basics of molecular biology is required to resolve the issues presented and to provide the requisite insight into the fundamentals of the genome, that is, the nature which is at the heard of the dispute between the parties. What follows represents the standard undisputed knowledge of those in the field of molecular biology as set forth in the parties' 56.1

Statements and expert declarations. Citations are also made to two established texts in the field: Bruce Alberts, et al, *Molecular Biology of the Cell* (4th ed. 2002) *("The Cell")* and James Watson, et al., *Molecular Biology* of *the Gene* (6th ed. 2008) (*"The Gene").*

1. DNA

DNA is a chemical molecule composed of repeating chemical units known as "nucleotides" or "bases." DNA is composed of four standard nucleotides: adenine, thymine, cytosine, and guanine. As shorthand, scientists denote nucleotides by the first letter of the names of their bases: "A" for adenine; "G" for guanine; "T" for thymine; and "C" for cytosine. These nucleotide units are composed of several chemical elements, namely carbon, hydrogen, oxygen, nitrogen, and phosphorus, and are linked together by chemical bonds to form a strand, or polymer, of the DNA molecule. Kay Decl. ¶¶ 14, 125; Linck Decl. ¶ 70.

Although it can exist as a single strand of nucleotides, DNA typically exists as a "double helix,"[4] consisting of two intertwined strands of DNA that are chemically bound to each other. This structure is possible because of a property of DNA known as "base pair complementarity" or "base pairing," in which adenine on one strand of DNA always binds to thymine on the other strand of DNA, and guanine on one strand always bind to cytosine on the other strand. Kay Decl. ¶ 129. For example, if a portion of one strand of DNA has the nucleotide sequence ACTCGT, the corresponding section of DNA on the complementary strand will have the nucleotide sequence TGAGCA.

Genes are basic units of heredity found in all living organisms and are responsible for the inheritance of a discrete trait. Sulston Decl. ¶ 11. In molecular terms, a gene is composed of several, typically contiguous, segments of DNA. Kay Decl. ¶ 142. Each gene is typically thousands of nucleotides long and usually "encodes" one or more proteins, meaning it contains the information used by the body to produce those proteins. Some of the segments of DNA within a gene, known as "exons" or "coding sequences," contain sequences necessary for the creation of a protein, while other segments of DNA, known as "introns," are not necessary for the creation of a protein.[5] See Mason Decl. ¶ 11; Kay Decl. ¶ 151; Schlessinger Decl. ¶ 14. DNA encodes proteins by way of three nucleotide combinations, termed "codons," that correspond to one of twenty amino acids that constitute the building blocks of proteins. Sulston Decl. ¶¶ 14-15. For example, the codon adenine-thymine-guanine (ATG) encodes the amino acid methionine. Kay Decl. ¶ 158. However, because there are only twenty different amino acids but 64 possible codons that can be derived from combinations of the four DNA nucleotides, most amino acids are encoded by more than one DNA codon. *The Gene* at 37 & Table 2-3.

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[4] It was the description of this famous "double-helix" structure that earned Watson and Crick the Nobel Prize.

[5] Introns can contain regulatory sequences that affect the body's rate of production of the protein encoded by a gene. Kay Decl. ¶ 151.

Together, the approximately 25,000 genes in the human body make up the human genome.[6] The genome, and the genes within it, are contained within almost every cell in the human body and define physical traits such as skin tone, eye color, and sex, in addition to influencing the development of conditions such as obesity, diabetes, Alzheimer's disease, and bipolar disorder. Mason Decl. ¶ 4-5; Sulston Decl. ¶¶ 10-11.

The linear order of DNA nucleotides that make up a polynucleotide, such as a gene, is referred to as the "nucleotide sequence," "DNA sequence," or "gene sequence."[7] Kay Decl. ¶ 126; Schlessinger Decl. ¶ 19; Linck Decl. ¶ 45; Sulston Decl. ¶ 16; Mason Decl. ¶ 13; Chung Decl. ¶ 10. Gene sequences constitute biological information insofar as they describe the structural and chemical properties of a particular DNA molecule and serve as the cellular "blueprint" for the production of proteins. Sulston Decl. ¶ 16; Kay Decl. ¶ 126; Schlessinger Decl. ¶ 19; Linck Decl. ¶¶ 45, 46. Genes and the information represented by human gene sequences are products of nature universally present in each individual, and the information content of a human gene sequence is fixed. While many inventive steps may be necessary to allow scientists to extract and read a gene sequence, it is undisputed that the ordering of the nucleotides is determined by nature. Sulston Decl. ¶ 10, 17; Ostrer Decl. ¶ 14; Chung Decl. ¶ 25; Ledbetter Decl. ¶ 27; Leonard Decl. ¶ 15.

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[6] Genome is defined as [t]he totality of genetic information belonging to a cell or an organism; in particular, the DNA that carries this information." *The Cell* at G:15.

[7] By analogy, if a gene is the equivalent of a word, then the nucleotide sequence is the equivalent of the word's spelling.

Scientists often use the term "wild-type" to refer to the "normal" human gene sequence, i.e. the sequence of a gene without any variations,[8] against which individuals' gene sequences are compared. Mason Decl. ¶ 17; Grody Decl. ¶ 46. Variations in the human genome are very common; aside from identical twins, the genomes of any two individuals are estimated to have one to five nucleotide differences for every 1000 nucleotides. Mason Decl. ¶ 14; Sulston Decl. ¶ 12.

Variations in the human genome, also known as "mutations," can occur at different scales. Small scale variations can be manifested as slight sequence differences between the same genes in different individuals. Thus, for example, if the wild-type sequence of a portion of a gene is represented by GACTCG, a variation of that sequence might omit the first C (resulting in GATCG) or contain an extra C at that point (resulting in GACCTCG) or reverse the order of two of the letters (e.g., GCATCG). Mason Decl. ¶ 16. Alternatively, there can be large scale variations, such as the addition or deletion of substantial chromosomal regions. Thus, a particular gene may omit several hundred letters at one point or may add several hundred letters where they do not normally exist in the wild-type gene sequence. Even larger variations, known as structural variants, also can occur, involving the deletion or duplication of up to millions of nucleotides. Extra copies or missing copies of the genome that are larger than 1000 nucleotides are called "copy number variants" ("CNVs"). Mason Decl. ¶ 15, 18.

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[8] At the same time there is an increasing recognition that the notion of a single "normal" gene sequence may not be entirely accurate in light of the high frequency of variations in a genets sequence between individuals. Mason Decl. ¶ 17. For purposes of this opinion, however, genes are treated as having a single "normal" DNA sequence.

Some of these mutations have little or no effect on the body's processes, while other mutations, including those that appear to correlate with an increased risk of particular diseases, do interfere with the body's processes.[9] There are also variants of uncertain significance ("VUS"): variants whose effect on the body's processes, if any, is currently unknown. Mason Decl. ¶ 19; Sulston Decl. ¶ 18; Kay Decl. ¶ 76.

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[9] The correlation between a particular mutation and disease susceptibility is not self-evident from the mutation itself; rather, extensive statistical analysis is required to identify which alterations in the nucleotide sequence correlate with a particular medical condition, a process which may take many years. Kay Decl. ¶ 190.

DNA as it is found in the human body - "native DNA" or "genomic DNA" is packaged, along with proteins, into complex structures known as chromosomes, which contain the vast majority of the genes located in the cells of the human body. Kay Decl. ¶ 131; Schlessinger Decl. ¶ 12. This mixture of DNA and proteins that makes up chromosomes is also referred to as chromatin. See *The Gene* at 135. Genes are organized on forty-six chromosomes (twenty-three of which are inherited from the mother, and twenty-three of which are inherited from the father) which together constitute the vast majority of the human genome.[10] Mason Decl. ¶ 5. The proteins within the chromosomes are bound[11] to the DNA molecules and modulate the structure and function of the DNA molecules to which they are associated. Kay Decl. ¶ 131; Schlessinger Decl. ¶ 12; *The Cell* at 198, 208, Fig. 4-24. This interaction between chromosomal proteins and native DNA is one method by which the body establishes which genes are inactive, which genes are active, and the level of activity.

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[10] A very small fraction of human genes are located in a cellular organelle known as the mitochondria. Kay Decl. ¶ 144; Schlessinger Decl. ¶ 23. Neither party appears to believe that a discussion of mitochondrial DNA bears much relevance to the legal issues presented.

[11] The ionic chemical bonds that exists between proteins and DNA molecules differ from the covalent chemical bonds which hold DNA itself together. See *The Cell* at 198 (describing DNA in the cell as "associated with proteins that fold and pack the fine DNA thread into a more compact structure."); id. at 208 Fig. 4-24 (demonstrating dissociation of histone proteins from DNA by high salt solution, indicating lack of covalent bond between DNA and histones).

Kay Decl. ¶ 132. Some DNA in the body also undergoes chemical modifications, such as methylation,[12] which can affect the level of activity of a gene, but does not affect the nucleotide sequence of the gene. Kay Decl. ¶ 132; Mason Supp. Decl. ¶ 22.

2. Extracted and purified DNA

Native DNA may be extracted from its cellular environment, including the associated chromosomal proteins, using any number of well-established laboratory techniques. Grody Decl. ¶ 13; Leonard Decl. ¶ 33. A particular segment of DNA, such as a gene, contained in the extracted DNA may then be excised from the genomic DNA in which it is embedded to obtain the purified DNA of interest. Kay Decl. ¶¶ 133, 137. DNA molecules may also be chemically synthesized in the laboratory. Kay Decl. ¶¶ 17, 133, 137.

Although the parties use the term "isolated DNA" to describe DNA that is separated from proteins and other DNA sequences, the term "isolated DNA" possesses a specific legal definition reflecting its use in the patents-in-suit. To avoid any confusion for purposes of this fact recitation, the term "extracted DNA" will be used to refer to DNA that has been removed from the cell and separated from other non-DNA materials in the cell (e.g., proteins); "purified DNA" will be used to refer to extracted DNA which has been further processed to separate the particular segment of DNA of interest from the other DNA in the genome; and "synthesized DNA" will be used to refer to DNA which has been synthesized in the laboratory.

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[12] Methylation refers to the addition of a small chemical group composed of one carbon atom and three hydrogen atoms (CH_3), known as a "methyl group," to the nucleotides of a segment of DNA. See *The Cell* at 430.

As noted above, native DNA, unlike purified or synthesized DNA, is not typically found floating freely in cells of the body, but is packaged into chromosomes. Kay Decl. ¶¶ 131, 148. However, when DNA is copied, or replicated, in preparation for cell division, short segments of DNA are dissociated from the chromosomal proteins, although they are still contained within the cell. Similarly, when a particular portion of DNA is transcribed into RNA, segments of DNA exist dissociated from the proteins normally bound to it. Mason Supp. Decl. ¶ 23.

Purified or synthesized DNA may be used as tools for biotechnological applications for which native DNA cannot be used. Kay Decl. ¶¶ 134, 138; Schlessinger Decl. ¶ 27. For example, unlike native DNA, purified or synthesized DNA may be used as a "probe,"[13] which is a diagnostic tool that a molecular biologist uses to target and bind to a particular segment of DNA, thus allowing the target DNA sequence to be detectable using standard laboratory machinery. Kay Decl. ¶ 135; Schlessinger Decl. ¶ 29. Purified or synthesized DNA can also be used as a "primer,"[14] to sequence a target DNA, a process used by molecular biologists to determine the order of nucleotides in a DNA molecule, or to perform polymerase chain reaction ("PCR") amplification, a process which utilizes target-DNA specific primers to duplicate the quantity of target DNA exponentially. Critchfield Decl. ¶ 40; Kay Decl. ¶ 184.

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[13] A probe is a DNA fragment that is usually between 100-1000 nucleotides long. Kay Decl. ¶ 135.

[14] A primer is a DNA fragment, usually between 15 and 30 nucleotides long, that binds specifically to a target DNA sequence. Kay Decl. ¶ 183.

During this process, the DNA molecule being used as a probe or a primer binds, or "hybridizes," to a specific nucleotide sequence of a DNA target molecule, such as the *BRCA1* or *BRCA2* gene. This sequence-specific binding of two strands of DNA results from the same base-pairing phenomenon which allows two complementary strands of DNA to form the double helix structure. As a result, a strand of isolated DNA being used as a primer with the sequence ATGTCG, for example, will bind specifically to the portion of the target DNA molecule containing the nucleotide sequence TACAGC. The hybridization of a primer or probe to a DNA target, such as *BRCA1* or *BRCA2*, results in the formation of a "hybridization product" that either acts as a substrate for the enzymes used in the sequencing or amplification reaction or permits the detection of the target DNA. See Kay Decl. ¶¶ 138, 183; Schlessinger Decl. ¶ 30; *The Gene* at 105-06; 113-15.

The utility of purified *BRCA1/2* DNA molecules as biotechnological tools therefore relies on their ability to selectively bind to native or isolated *BRCA1/2* DNA molecules, which ability is a function of the isolated DNA's nucleotide sequence. Kay Decl. ¶ 138.

3. RNA

Ribonucleic acid ("RNA") is another nucleic acid found in cells. Like DNA, an RNA molecule is composed of a combination of four different nucleotides, three of which are the same bases incorporated into DNA: adenine, cytosine, and guanine. Unlike DNA, however, RNA utilizes uracil as the fourth nucleotide base, rather than thymine. In addition, the sugar-phosphate backbone in RNA is chemically different from the sugar-phosphate backbone of DNA. Kay Decl. ¶ 170.

The creation of proteins, which do the work of the body, comprises two steps: transcription and translation. Transcription is the process by which a temporary copy of a particular DNA sequence, in the form of an RNA molecule, is generated. Mason Decl. ¶¶ 11-12; Kay Decl. ¶¶ 149, 150. During transcription, a discrete segment of DNA unwinds itself inside the cell and the bases of the DNA molecule act as "clamps" that hold the bases of the newly forming RNA molecule in place while the chemical bonds of its sugar-phosphate backbone are formed. Kay Decl. ¶ 150. Each nucleotide in the DNA strand corresponds to a nucleotide to be incorporated into the newly forming RNA molecule: adenine on the DNA molecule binds to and thereby acts as a clamp for RNA nucleotide uracil, thymine for adenine, guanine for cytosine, and cytosine for guanine. Kay Decl. ¶ 150. This newly generated RNA is termed "pre-messenger RNA" or "pre-mRNA" and, like the DNA from which it was generated, contains both introns and exons. In a process known as "splicing," the introns are physically cut out of the pre-mRNA by the cell and the remaining RNA segments containing the exons are rejoined, or "ligated," together in consecutive order to form the final "messenger RNA," or "mRNA." Mason Decl. ¶ 11; Kay Decl. ¶ 151; Schlessinger Decl. ¶ 14. Pre-mRNAs can also undergo a process known as "alternative splicing," in which different combinations of exons from the same pre-mRNA molecule are ligated together to yield different final mRNA products.[15] Kay Decl. ¶ 152; Schlessinger Decl. ¶ 14.

During translation, an mRNA molecule serves as a template for the assembly of a protein. Kay Decl. ¶ 157. In a process that parallels the transcription of DNA, the mRNA bases, along with other proteins in the cell, serve as clamps to hold the corresponding amino acids in place while the chemical bonds between the individual amino acids are formed. Kay Decl. ¶ 157. The three-nucleotide codons originally found in DNA and copied into mRNA determine which amino acids are incorporated into the protein and the order in which they are incorporated. Kay Decl. ¶ 157.

4. cDNA

Complementary DNA, or "cDNA," is a type of DNA molecule generated from mRNA during a process known as "reverse transcription" which is catalyzed by a protein known as "reverse transcriptase." cDNA derives its name from the fact that it is "complementary" to the mRNA from which it is produced - that is, each base in the cDNA can bind to the corresponding base in the mRNA from which it is generated. Kay Decl. ¶ 161. Because it is derived from mRNA, a cDNA molecule represents an exact copy of one of the protein coding sequences encoded by the original genomic DNA. Leonard Decl. ¶ 75. In this respect, cDNA contains the identical protein coding informational content as the DNA in the body, even though differences exist in its physical form. Mason Decl. ¶ 32.

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[15] For example, a pre-mRNA molecule containing exons ("E") numbered 1-6, with introns ("I") between each axon whose structure is represented as follows: El+Il+E2+12+E3+13+E4+14+ES+IS+E6. After splicing, the introns would be removed to form an mRNA composed only of exons: E1+E2+E3+E4+E5+E6. On the other hand, the same pre-mRNA molecule might undergo alternative splicing to form final mRNAs with a variety of different exon compositions: for example, E1+E2+E5; El+E3+E6: and E1+E4+E6.

During reverse transcription, each base of the mRNA serves as a clamp for its complementary nucleotide to be incorporated into the new cDNA molecule while the chemical bonds between the nucleotides of the cDNA strand are formed. Much like transcription, uracil on the mRNA binds to and thereby acts as a clamp for the nucleotide adenine, adenine for thymine, guanine for cytosine, and cytosine for guanine. Kay Decl. ¶ 165. The synthesis of cDNA from very long mRNA molecules, such as *BRCA1* and *BRCA2*, often does not result in a cDNA strand that is as long as the mRNA chain. Kay Decl. ¶ 166.

cDNA is typically generated by scientists in a laboratory. Kay Decl. ¶ 164, Linck Decl. ¶ 48. However, naturally occurring cDNAs, known as "pseudogenes," exist in the human genome and are structurally, functionally, and chemically identical to cDNAs made in the laboratory. Mason Supp. Decl. ¶¶ 18-21; Nussbaum Decl. ¶¶ 41-42.

cDNA possesses certain structural and functional differences from native DNA. In contrast to most forms of native DNA, cDNA does not contain non-coding intronic sequences because it *is* derived from mRNA *in* which the introns have been removed. As a result, the production of proteins from cDNA does not require RNA splicing, in contrast to the production of proteins from native DNA as described above. Some cDNAs cannot be used to produce proteins without the addition of certain regulatory sequences, although other cDNAs possess some of the necessary regulatory sequences. cDNAs also usually contain nucleotides corresponding to the so-called "poly A tail" sequence found in mRNA, which native DNA does not possess. In addition, as mentioned above, native DNA is often (although not always) chemically modified in the body, e.g., by methylation, while cDNA generated in the laboratory is not so modified. Kay Decl. ¶¶ 168, 169; Mason Supp. Decl. ¶¶ 18-22; Nussbaum Decl. ¶¶ 41-42. cDNA also differs from mRNA in that it is a more stable compound and requires both transcription and translation to produce protein, rather than simply translation, as is the case with mRNA. Kay Decl. ¶ 171.

Much like purified DNA, cDNA can be used as a tool for biotechnological and diagnostic applications for which native DNA cannot be used. Kay Decl. ¶ 162. In addition, a scientist seeking to learn more about a protein of interest may transfer a cDNA encoding the protein into a recipient cell that does not normally express that protein. If the cDNA is operatively linked to particular "promoter" sequences that initiate transcription from the cDNA, the recipient cell will then express the protein of interest. Kay Decl. ¶ 163.

5. DNA sequencing

DNA sequencing is the process by which one "reads," or determines the ordering of the nucleotides within a DNA molecule. Sulston Decl. ¶ 20; Kay Decl. ¶ 138. In the context of a gene or a portion of the genome, sequencing is designed to illuminate the information that nature has dictated in that person's genome, and the sequencing process, by design, does not alter the information content of the native DNA sequence. Sulston Decl. ¶ 27; Mason Decl. ¶ 32. In that respect, sequencing is analogous to examining something through a microscope insofar as it makes visible something that exists in nature but is too small to be seen otherwise. Mason Decl. ¶ 23. Gene sequencing is used in diagnostic testing, such as Myriad's tests, to determine whether a gene contains mutations that have been associated with a particular condition. Sulston Decl. ¶ 24; Chung Decl. ¶ 10; Swisher Decl. ¶¶ 23-26; Mason Decl. ¶ 21. These mutations, along with any association with a propensity to develop a particular disease, are caused by nature. Chung Decl. ¶ 10; Mason Decl. ¶ 20; Sulston Decl. ¶¶ 19, 27; Ledbetter Decl. ¶ 26. Therefore, the significance of any person's gene sequence, including its relationship to any disease, is dictated by nature. Mason Decl. ¶ 32.

Sequencing is often used to identify single nucleotide substitutions or the insertion or deletion of a small number of nucleotides in a gene. Swisher Decl. ¶ 23; Kay Decl. ¶ 180. However, even full sequencing of an entire gene can miss large genomic rearrangements in which whole sections of the gene have been deleted or moved to a different part of the genome. Other tests have been developed that better detect these large rearrangements. Swisher Decl. ¶ 24; Ledbetter Decl. ¶¶ 16-17.

Sequencing native DNA first requires that cells of a tissue sample[16] be broken open to permit extraction of the DNA contained within the cells. Sulston Decl. ¶ 25. The extracted DNA of the entire genome contains over three billion nucleotides, of which the gene of interest comprises a very small portion. Kay Decl. ¶ 178. *BRCA1/2* sequencing by Myriad follows the typical process for sequencing extracted genomic DNA, which begins with obtaining a sufficient quantity of the *BRCA1/2* genomic DNA to permit its sequencing. Critchfield Decl. ¶ 40.

Under the current state of the art, the only practical way to obtain a sufficient amount of *BRCA1/2* genomic DNA for mutation detection purposes is to PCR amplify the genomic DNA in segments. Critchfield Decl. ¶ 40. In order to design the necessary primers to PCR amplify the correct region of the genome, at least a portion of the sequence of the target DNA molecule must be known. Kay Decl. ¶ 184. Typically, each exon of the *BRCA1/2* genes, including a small adjacent portion of the flanking introns, is separately amplified by PCR into one or more amplified DNA fragments, also called "amplicons." The *BRCA1* and *BRCA2* genes have a total of 48 coding exons containing over 15,700 nucleotide base pairs. More than 50 amplicons are typically produced as part of Myriad's *BRCA1/2* testing. Critchfield Decl. ¶ 40.

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[16] Various types of patient samples can be used, e.g., blood, tumor tissue, or non-tumor tissue. Kay Decl. ¶ 186.

Following PCR amplification of the target DNA, a sequencing reaction is performed to determine the nucleotide sequence of the amplicon. Kay Decl. ¶ 183. As with PCR, at least some of the target sequence must be known in order to design a primer specific to the target DNA to be sequenced. Kay Decl. ¶¶ 177, 179, 183. For this reason, primers that bind only to specific DNA sequences in the *BRCA1I* and *BRCA2* genes permit the analysis of a patient's native DNA sequence to determine *if* the nucleotide composition is the same or different from the nucleotide composition of the normal *BRCA1* and *BRCA2* gene. Kay Decl. ¶ 187. Gene sequencing also sometimes utilizes cDNA as the DNA template. Leonard Decl. ¶ 75.

The techniques required for gene sequencing are well-known and understood by scientists skilled in molecular biology, and scientists and clinicians sequence and analyze genes literally every day. Chung Decl. ¶¶ 10-11; Mason Decl. ¶ 22; Hegde Decl. ¶¶ 6-7. However, because sequencing requires knowledge of the sequence of a portion of the target sequence, some ingenuity and effort is required for the initial sequencing of a target DNA. See Kay Decl. ¶ 183; Klein Decl. ¶ 32-34.

C. The Development of the Patents-in-Suit

Breast cancer is the most frequently diagnosed cancer worldwide and is the leading cause of cancer death for women in Britain and the second leading cause of cancer death for women in the United

States. Parthasarathy Decl. ¶ 8.[17] Ovarian cancer is the eighth most common cancer in women and causes more deaths in the Western world than any other gynecologic cancer. Swisher Decl. ¶ 10.

Throughout the 1980s, organizations dedicated to breast cancer awareness began efforts to increase public and governmental awareness of the breast cancer epidemic. In 1991, the U.S. Department of Defense created a research program devoted to breast cancer research. Over the years this funding has grown from less than $90 million during the fiscal year 1990 to more than $2.1 billion during the fiscal year 2008. Parthasarathy Decl. ¶ 10.

Throughout the 1980s, scientists from the United States, England, France, Germany, Japan, and other countries sought to be the first to identify DNA nucleotide sequences associated with breast cancer. Parthasarathy Decl. ¶ 11. In 1989, various European and American research laboratories participated in the International Breast Cancer Linkage Consortium (the "Consortium"), and in 1990, a group of researchers led by Mary-Claire King ("Dr. King") at the University of California, Berkeley, published a landmark paper demonstrating for the first time that a gene linked to breast cancer, whose sequence was unknown but which was later designated Breast Cancer Susceptibility Gene 1 *(BRCA1)*, was located on a region of chromosome 17.

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[17] Dr. Parthasarathy has researched the development of genetic testing for breast and ovarian cancer in the United States and Britain and has interviewed over 100 individuals involved in the process, including research scientists, officials at research institutions, health care professionals, patent office officials, bioethicists, and journalists. Parthasarathy Decl. ¶ 6.

See Jeff M. Hall, et al., Linkage of Early-Onset Familial Breast Cancer to Chromosome 17q21, 250 Science 1684-89 (1990); Parthasarathy Decl. ¶ 11. Soon afterwards, research intensified as teams around the world, including groups led by Dr. King, Dr. Mark Skolnick ("Dr. Skolnick") (co-founder of Myriad), and Dr. Michael Stratton ("Dr. Stratton") (Institute for Cancer Research, London ("ICR")), focused in on this region of the genome in an attempt to be the first to determine the DNA sequence of *BRCA1*. Parthasarathy Decl. ¶ 11.

Dr. Skolnick, a 1968 economics graduate of the University of California, Berkeley, had become interested in the application of demography to the study of genetics while doing research for his Ph.D. in genetics, which he received from Stanford University in 1975. While reconstructing genealogies in Italy, he met three Mormons who were microfilming parish records and from whom he learned of the resources of the Utah Genealogical Society in Salt Lake City. Thereafter, in 1973, after an inquiry from the organizers of a cancer center at the University of Utah, Dr. Skolnick suggested linking the Utah Mormon Genealogy with the Utah Cancer Registry. To further this effort, a familial cancer screening clinic was established and a program for mapping genes was developed. Skolnick Decl. ¶¶ 7, 11, 12.

Following publication of the King group's study relating to *BRCA1* in the fall of 1990, Dr. Skolnick and his collaborators concluded that additional resources would be required to compete with the team of Dr. Francis Collins, which had received a substantial grant from the National

Institutes of Health ("NIH"), Skolnick Decl. ¶¶ 11 13, 14, and in 1991 Myriad was founded by Dr. Skolnick and a local venture capital group interested in genetics. Myriad received $5 million in funding in 1992, $8 million in 1993, and $9 million in 1994. Skolnick Decl. ¶ 16.

Locating the *BRCA1* gene relied on the use of linkage analysis, in which correlations between the occurrence of cancer and the inheritance of certain DNA markers among family members were used to identify, or "map," the physical location of, the *BRCA1* gene within the human genome. See '282 patent, col. 7:39-52. Once the physical location had been narrowed down to a sufficiently small region of the genome, Myriad was able to directly analyze the sequence of the DNA in this region and identify the nucleotides comprising the *BRCA1* gene. See '282 patent, col. 7:53-8:7. Successful linkage analysis requires large and genetically informative families, or kindreds, and detailed family information, such as detailed genealogical records, are an important component to this analysis. Shattuck Decl. ¶¶ 10, 13; '282 patent, col. 8:16-29.

In September 1994, the group at Myriad, along with researchers from the National Institute for Environmental Health Sciences ("NIEHS") (a subdivision of the NIH), the University of Utah, McGill University, and Eli Lilly and Company announced that they had sequenced the *BRCA1* gene. See Yoshio Miki, et al., A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene *BRCA1*, 266 Science 66-71 (1994). In addition to funding the six NIEHS researchers who participated in the identification of *BRCA1*, the NIH had also provided approximately $2 million in funding to the University of Utah.[18] See id. at 71 n.52; Parthasarathy Decl. ¶ 18. According to one analysis, the NIH contributed one-third of the funding for the identification of *BRCA1*. Parthasarathy Decl. ¶ 18.

A dispute subsequently arose between Myriad and the NIH over the NIEHS scientists' exclusion as co-inventors on the *BRCA1* patents. Parthasarathy Decl. ¶ 19. The NIH maintained that its scientists had conducted some of the most important work leading up to the sequencing of the gene, including identifying the sequences of two of the *BRCA1* gene fragments and assembling the complete *BRCA1* sequence. Id. Myriad agreed to include the names of the NIEHS researchers as inventors on its patent application and pay inventors' royalties, although no payments appear to have been made as of 2005. Id.

Following the isolation of *BRCA1*, scientists continued to search for a second gene also believed to be linked with breast and ovarian cancer.[19] Parthasarathy Decl. ¶ 12. Myriad collaborated with several research groups, including scientists at the University of Laval in Quebec, Canada, the Hospital for Sick Children in Toronto, Canada, and the University of Pennsylvania in their search for this second gene. It also collaborated with a team of researchers led by Dr. Stratton at the ICR which, in November 1995, identified a mutation in breast cancer patients that appeared to be located in the as-yet unpublished *BRCA2* gene. Dr. Stratton ended the collaboration with Myriad upon learning of Myriad's plans to patent the *BRCA2* gene sequence. Sulston Decl. ¶ 30.

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[18] According to the description of author associations, the first and second authors of the paper were associated with the University of Utah.

[19] The same positional cloning approach utilized to isolate the *BRCA1* gene was relied on to isolate the *BRCA2* gene. Tavtigian Decl. ¶ 4.

On December 21, 1995, Myriad filed for patents on the *BRCA2* gene in both the U.S. and Europe. Tavtigian Decl. ¶ 5. The next day, the Stratton group published its identification of the *BRCA2* gene in the journal *Nature*, and Myriad submitted the sequence of *BRCA2* to GenBank, an international depository of gene sequence information. Parthasarathy Decl. ¶ 12; Tavtigian Decl. ¶ 9; Richard Wooster, et al., Identification of the Breast Cancer Susceptibility Gene *BRCA2*, 378 Nature 789-92 (1995). Subsequent analysis of the *BRCA2* sequence from the Stratton group indicated that while they had correctly sequenced the primary portion of the *BRCA2* gene, their published sequence had errors in both ends of the *BRCA2* gene. Tavtigian Decl. ¶¶ 7-10. Nonetheless, the consensus among the scientific community is that the Stratton group, rather than Myriad, was the first to sequence the *BRCA2* gene. Parthasarathy Decl. ¶ 13.

The isolation of the *BRCA1/2* genes required considerable effort on the part of Myriad and its collaborators as well as ingenuity in overcoming technical obstacles associated with the isolation process. However, the process and techniques used were well understood, widely used, and fairly uniform insofar as any scientist engaged in the search for a gene would likely have utilized a similar approach. Parthasarathy Decl. ¶ 19; Tavtigian Decl. ¶ 13.

D. Application of the Patents-in-Suit

Mutations in the *BRCA1/2* genes correlate with an increased risk of breast and ovarian cancer. Women with *BRCA1* and *BRCA2* mutations face up to an 85% cumulative risk of breast cancer, as well as up to a 50% cumulative risk of ovarian cancer. Love Decl. ¶ 10; Parthasarathy Decl. ¶ 9. In addition, among the 10-15% of ovarian cancer cases that are inherited genetically, 80% of women diagnosed under the age of 50 carry mutations in their *BRCAl* genes and 20% carry mutations in their *BRCA2* genes. The women with inherited *BRCA1* mutations have a 40-52% cumulative risk of ovarian cancer by the time they reach 70 years old. For women with inherited *BRCA2* mutations, the risk is approximately 15-25%. Swisher Decl. ¶ 11. Male carriers of mutations are also at an increased risk for breast and prostate cancer. Love Decl. ¶ 10.

The existence of *BRCA1/2* mutations is therefore an important consideration in the provision of clinical care for breast and/or ovarian cancer. A patient will not only learn of her risk for hereditary breast and ovarian cancer, but also can gain information that may be useful in determining prevention and treatment options. This information is useful for women who are facing difficult decisions regarding whether or not to undergo prophylactic surgery, hormonal therapy, chemotherapy, and other measures. Swisher Decl. ¶ 12; Love Decl. ¶ 11. Testing results for the *BRCA1/2* genes can be an important factor in structuring an appropriate course of cancer treatment, since certain forms of chemotherapy can be more effective in treating cancers related to *BRCA1/2* mutations. Swisher Decl. ¶ 13; Love Decl. ¶ 18.

1. Myriad's BRCA1/2 testing

Myriad offers multiple forms of *BRCA1/2* testing to the general public. Its standard test, called Comprehensive BRACAnalysis, originally only consisted of the full sequencing of the *BRCA1/2* genes. Swisher Decl. ¶ 29-30; Reich Decl. ¶ 10; Parthasarathy Decl. ¶ 26; Critchfield Decl. ¶ 49. In 2002, Myriad supplemented its full sequencing analysis with a large rearrangement panel ("LRP") for detecting five common large rearrangement mutations which is now included in the Comprehensive BRACAnalysis. Critchfield Decl. ¶¶ 49, 51. In 2006, Myriad began offering a supplemental test to Comprehensive BRACAnalysis called the BRACAnalysis Rearrangement Test ("BART"), which, according to Myriad, can detect virtually all large rearrangement mutations in the *BRCA1* and *BRCA2* genes.[20] Swisher Decl. ¶¶ 29-30; Reich Decl. ¶ 10; Parthasarathy Decl. ¶ 26; Critchfield Decl. ¶ 51.

2. Funding for Myriad' s BRCA1/2 tests

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[20] Myriad also offers other more limited forms of *BRCAI/2* genetic testing. Swisher Decl. ¶¶ 29-30; Reich Decl. ¶ 10; Parthasarathy Decl. ¶ 26.

The Myriad tests are available to clinicians and patients at a cost of over $3000 per test. In 2006, the total cost to Myriad of providing these tests was $32 million with resulting revenues of $222 million. See Myriad Genetics, Inc., Annual Report (Form 10-K), at 27 (Aug. 28, 2008). In Ontario, where the regional public healthcare plan is ignoring Myriad's patent, the testing for breast cancer is performed for a third of Myriad's cost. See CBC News, Ontario to Offer New Genetic Test for Breast, Ovarian Cancer (Jan. 8, 2003), available at http://www.cbc.ca/health/story/2003/01/06/test_genetic03010 6.html.

Plaintiffs have noted several instances where women have been unable to obtain funding for all of Myriad's testing services. For example, Myriad refused to process Ms. Ceriani's sample because it did not accept coverage by Ms. Ceriani's insurance carrier. Unable to pay for Myriad's tests, and unable to find scholarship programs to fund her testing, Ms. Ceriani has not been tested. Ceriani Decl. ¶¶ 5-7. Ms. Fortune's insurance carrier is not accepted by Myriad, and Ms. Fortune is also unable to pay the full out-of-pocket cost of Myriad's test. Fortune Decl. ¶ 5.

Myriad's BART test is not covered by a number of insurers, and unless a patient is one of a limited number of "high risk patients" who meet certain clinical criteria established by Myriad, a patient must pay an extra fee for BART testing. Swisher Decl. ¶¶ 29-30; Reich Decl. ¶ 10; Parthasarathy Decl. ¶ 26; Critchfield Decl. ¶ 52. As a result of the cost of BART testing, the test is unavailable to women who would otherwise choose to utilize the test. Swisher Decl. ¶¶ 30-31; Reich Decl. ¶ 10. For example, Ms. Raker is unable to afford the extra cost for BART testing and has not been tested for large genomic rearrangements, despite the advice of her genetic counselor. Raker Decl. ¶¶ 7-11. Similarly, Ms. Thomason has been unable afford the BART testing recommended by her genetic counselor. Thomason Decl. ¶¶ 6-9.

Myriad has pursued Medicaid coverage for years, but has been unable to secure "participating provider" status in 25 states which would allow it to offer testing to that state's Medicaid patients. Myriad also has a financial assistance program which provides free testing to low-income and uninsured patients who meet certain economic and clinical requirements. In addition, Myriad provides free testing to independent non-profit institutions. In particular, Ms. Ceriani may be eligible to receive BRACAnalysis testing at no charge through the non-profit organization Cancer Resource Foundation, for which Myriad has provided free testing since 2009. Rusconi Decl. ¶¶ 4-6; Critchfield Decl. ¶ 33; Ogaard Decl. ¶¶ 4-6. Currently, 90% of the tests Myriad performs are covered by insurance at over 90% of the test cost. Critchfield Decl. ¶ 1 32, 33, 52, 53.

A number of researchers, clinicians, and molecular pathologists have the personnel, equipment, and expertise to sequence and analyze genes, including the *BRCA1* and *BRCA2* genes, at a lower cost than Myriad's testing. Kazazian Decl. ¶¶ 8, 11; Matloff Decl. ¶ 12; Ostrer Decl. ¶¶ 8-9; Ledbetter Decl. ¶¶ 16-18. For example, the *BRCAI/2* testing previously conducted by the Yale DNA Diagnostics Laboratory and the University of Pennsylvania Genetic Diagnostic Laboratory ("GDL") cost less than what Myriad charges, and testing by OncorMed, a one-time competitor, was cheaper than Myriad's testing. Matloff Decl. ¶ 7; Kazazian Decl. ¶ 8; Parthasarathy Decl. ¶ 24. However, on a "cost per exon" basis, Myriad's BRACAnalysis test costs less than testing for other genes performed by the GDL at the University of Pennsylvania and Drs. Ledbetter and Warren at Emory University. See infra; Critchfield Decl. ¶ 35.

3. Myriad's enforcement of the Patents-in-suit

During the mid-to-late-1990s, Drs. Kazazian and Ganguly offered, for a fee, screening services for *BRCA1* mutations through the GDL at the University of Pennsylvania. Kazazian Decl. ¶ 4; Ganguly Decl. ¶ 3. The screening methodology utilized by Drs. Kazazian and Ganguly differed from the testing method used by Myriad, but involved using isolated DNA encoding *BRCA1* or *BRCA2.* Kazazian Decl. ¶ 9; Parthasarathy Decl. ¶ 23. At some point during this period, Dr. Skolnick advised Dr. Kazazian that Myriad planned to stop the *BRCA1/2* testing being conducted at the GDL. Kazazian Decl. ¶ 6. On May 29, 1998, Myriad offered Dr. Kazazian a collaborative license in connection with the '473, '999, '001, '282, and '441 patents. Ganguly Decl. Ex. 2. However, the license covered only single mutation tests and multiple mutation panels of up to four mutations to allow for testing of patients of Ashkenazi Jewish descent. Ganguly Decl. ¶ 5. Myriad subsequently sent cease and desist letters to Dr. Kazazian and the University of Pennsylvania. On August 26, 1998 O'Melveny & Myers LLP gave notice to Dr. Kazazian of infringement in the absence of a license. Ganguly Decl. Ex. 3. Myriad subsequently sued the University of Pennsylvania in November 1998 for infringement of the patents-in-suit. See Myriad Genetics v. Univ. of Pennsylvania, 2: 98-cv-00829 (D. Utah) (filed November 19, 1998). On June 10, 1999, Myriad's general counsel, Christopher Wright, sent a letter to the University of Pennsylvania seeking written assurances that Dr. Kazazian and the University of Pennsylvania had ceased *BRCA1/2* clinical testing. Ganguly Decl. Ex. 4. This demand was repeated in a September 22, 1999 letter from Myriad to the University of Pennsylvania. Ganguly Decl. Ex. 6.

As a result of Myriad's efforts to enforce its patents against the University of Pennsylvania, the GDL no longer conducts *BRCA1/2* screening for research or as part of its clinical practice. Kazazian Decl. ¶ 5; Ganguly Decl. ¶¶ 8-9; Parthasarathy Decl. ¶ 28. However, sometime between 1999 and 2000, Dr. Critchfield, on behalf of Myriad, informed Dr. Kazazian that he is free to conduct academic research on the *BRCA1/2* genes, including sequencing the genes and detecting mutations in the genes. Critchfield Decl. ¶ 22.

In May 1998, Myriad offered Dr. Ostrer a license agreement to conduct diagnostic *BRCA1/2* genetic testing. The proposed license would permit Dr. Ostrer to conduct single mutation tests and multiple mutation panels (up to four mutations) for patients of Ashkenazi Jewish descent only.

Dr. Ostrer declined the offer as too narrow to allow him to perform any meaningful *BRCA1/2* testing. Ostrer Decl. ¶ 7.

On September 15, 1998, Myriad also notified Dr. Barbara Weber ("Dr. Weber"), a principal investigator on the Cancer Genetics Network Project ("CGNP") sponsored by the National Cancer Institute ("NCI"), that Myriad's patent position might impact research sponsored by NCI. As a result of that letter, the GDL at the University of Pennsylvania ceased conducting *BRCA1/2* analysis for Dr. Weber. Ganguly Decl. ¶ 12, Ex. 7. According to Myriad, the GDL's involvement in CGNP was to provide DNA testing on *BRCA1/2* genes for a fee, similar to the activity of any commercial core lab. Critchfield Decl. ¶ 21. In September 1999, Myriad also requested that Georgetown University, one of the other cancer centers participating in the CGNP, to cease sending genetic samples to the GDL for *BRCA1/2* analysis. Ganguly Decl. ¶ 13.

In December 2000, the director of the Yale DNA Diagnostics Lab received a cease and desist letter concerning *BRCA1/2* genetic testing being conducted by the lab. As a result of the letter, the lab ceased *BRCA1/2* genetic testing. Matloff Decl. ¶ 7. In 2005, Dr. Matloff sought permission from Myriad for the Yale DNA Diagnostics Lab to conduct screening for mutations caused by large rearrangements, which Myriad was not conducting at the time. Her request was denied. Matloff Decl. ¶ 8.

Myriad was also involved in a series of lawsuits in the late 1990s against Oncormed, another company undertaking BRCA-related testing, regarding patents that covered various aspects of the *BRCA1* gene sequence. Parthasarathy Decl. ¶ 27. Myriad eventually purchased Oncormed's patents and testing services in 1998. Id.

E. Disputed Issues

1. The impact of Myriad's patents on BRCA1/2 testing

According to Plaintiffs, Myriad's patents and its position as the sole provider of *BRCA1/2* testing has hindered the ability of patients to receive the highest quality breast cancer genetic testing and has impeded the development of improvements to *BRCA1/2* genetic testing. Plaintiffs first note deficiencies in the genetic testing services offered by Myriad, alleging that in the several years prior to the addition of the LRP, the testing done by Myriad did not reveal all known mutations in the *BRCA1/2* genes or utilize known methodologies that would have revealed these additional mutations.[21] Chung Decl. ¶ 19; Matloff Decl. ¶ 8; Swisher Decl. ¶ 26; Ledbetter Decl. ¶ 16; Parthasarathy Decl. ¶ 29. As a result, Myriad's test may have reported false negative results during this period. Plaintiffs also cite a study published in 2006 in the Journal of the American Medical Association that concluded that 12% of those from high risk families with breast cancer and with negative test results from Myriad carried cancer-predisposing genomic deletions or duplications in one of those genes. Swisher Decl. ¶¶ 25-26. Plaintiffs also note that the sensitivity and specificity of the BART test has not been validated by comparing the results of BART testing with Multiplex Ligation Dependent Probe Amplification ("MLPA") testing commonly used by researchers. Swisher Decl. ¶¶ 32, 33.

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[21] For example, the Myriad test received by Ms. Thomason, Ms. Raker, and Ms. Limary did not look for all known large rearrangements in the *BRCA* genes. Thomason Decl. ¶ 6; Raker Decl. ¶¶ 7-8; Limary Decl. ¶ 7.

According to Plaintiffs, other labs are in a position to offer more comprehensive testing than Myriad's standard testing services and would use newer testing methods with improved testing quality and efficiency. These labs would also include large rearrangement testing after a negative test result is received from full sequencing. Ledbetter Decl. ¶¶ 17-18; Chung Decl. ¶ 18; Ostrer Decl. ¶ 9. In addition, labs would perform genetic testing on tumor specimens preserved in paraffin from deceased family members, which Myriad does not regularly perform even though, according to Plaintiffs, such testing can often provide valuable genetic information for living relatives and is often necessary for accurate test interpretation. Chung Decl. ¶ 24.

According to Myriad, however, its full sequencing test has been recognized as the "gold standard" for *BRCA1/2* mutation testing, and it continues to improve its testing process. Critchfield Decl. ¶ 37. Myriad contends that it researched and developed a commercially viable high quality test for detecting large rearrangements as soon as it and the research community recognized the need for such testing, and continues work towards a test capable of detecting all large rearrangement mutations, including extremely rare ones. Critchfield Decl. ¶¶ 49, 50. According to

Myriad, *BRCA1/2* studies conducted by outside researchers confirmed that the BART test exhibited superior performance over other methods for mutation detection, including the MLPA kit often used by academic researchers.[22] Critchfield Decl. ¶ 51.

According to Plaintiffs, the lack of independent *BRCA1/2* analysis also undermines the ability of the scientific community to determine the meaning of VUS results, which are reported disproportionately for members of minority groups, and whose significance would be more extensively analyzed by other labs. Chung Decl. ¶ 20-21; Ostrer Decl. ¶ 12; Matloff Decl. ¶ 9. Myriad, however, asserts that it has undertaken significant efforts to determine the clinical importance of VUSs by establishing an in-house review committee for variant classification and developing a systematic approach to providing clinical interpretations for detected sequence variants based on generally accepted scientific data and analysis of its own database. In addition, clarification of any VUS previously reported to a patient is immediately provided to the patient and her doctor. According to Myriad, the VUS reporting rate has decreased markedly, with a 50% decrease in major ethnic groups between 2002 and 2006, and a total of 850 VUSs for about 21,000 patients have been clarified, including 502 VUSs for 13,127 patients since the beginning of 2008. Myriad also asserts that it has made critical data available to researchers to assist in the analysis of VUSs and which have the potential of improving the diagnostic testing for other genes. Critchfield Decl. ¶¶ 57-59.

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[22] In addition, Myriad states that the MLPA kit is for research use only, is not approved for clinical testing by the FDA, and is incapable of detecting certain smaller rearrangements. Critchfield Decl. ¶¶ 49, 50.

Plaintiffs contend that as a result of the patents-in-suit, *BRCA1/2* genetic testing is one of the very few tests performed as part of breast cancer care and prevention for which a doctor or patient cannot get a second confirmatory test done through another laboratory. Love Decl. ¶ 12. In particular, women who receive a positive result cannot confirm the lab's findings or seek a second opinion on the interpretation of those results.[23] Ledbetter Decl. ¶ 23; Ostrer Decl. ¶ 11. According to Myriad, absent any doubts regarding the accuracy of the original test, re-sequencing the patient's genes by another laboratory would be an unnecessary waste of resources, and Myriad has never prohibited a second interpretation of the results of its diagnostic tests. Critchfield Decl. ¶ 64; Reilly Decl. ¶¶ 54, 55. In addition, there are multiple laboratories available to conduct confirmatory *BRCA1/2* testing pursuant to patent licenses granted by Myriad, including both the University of Chicago Genetic Services Laboratories and Yale DNA Diagnostic Laboratories.

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[23] For example, Ms. Girard sought but was unable to obtain confirmatory testing of her Myriad test results that indicated the presence of a deleterious mutation in her *BRCA2* gene. A second opinion would also be important for her immediate family's screening options. Girard Decl. ¶¶ 4-9. Similarly, Ms. Ceriani and Ms. Fortune would both want a second opinion concerning their *BRCA1/2* status before taking major surgical steps. Ceriani Decl. ¶¶ 9, 11; Fortune Decl. ¶ 7.

Critchfield Decl. ¶ 62. That confirmatory testing, however, is limited to the confirmation of certain, specific positive test results; the remaining types of positive test results as well as all negative test results are excluded from such testing services. Matloff Decl. ¶¶ 9, 10.

Whether the patents at issue impact the testing for *BRCA1/2* mutations favorably or unfavorably is an issue of factual dispute not resolvable in the context of the instant motions.

2. The impact of gene patents on the advancement of science and medical treatment

There exists a deep disagreement between the parties concerning the effects of gene patents on the progression of scientific knowledge.

According to Plaintiffs, data sharing is the key to the future of genetic discoveries and bioinformatics, and gene patents impede research aimed at identifying the role of genes in medical conditions. Sulston Decl. ¶¶ 36, 38. Plaintiffs assert that this understanding has wide acceptance, noting that from the beginning of the Human Genome project,[24] most scientists and even some private companies recognized the importance of keeping the genome freely available to all. For example, in 1994, the pharmaceutical company Merck funded a massive drive to generate gene sequences and place them into public databases, thereby making them difficult to patent. Sulston Decl. ¶¶ 22, 29. In 1996, a group of 50 of the most prominent geneticists who were involved with the sequencing of the human genome adopted the Bermuda principles which included the mandate that all "human genome sequence information should be freely available and in the public domain in order to encourage research and development and to maximize its benefit to society." Sulston Decl. ¶ 33. The proliferation of intellectual property rights directed to genetic material has also been postulated to contribute to a phenomenon dubbed "the tragedy of the anti-commons," in which numerous competing patent rights held by independent parties prevents anyone party from engaging in productive innovation. See, e.g., Michael A. Heller & Rebecca S. Eisenberg, Can Patents Deter Innovation? The Anticommons in Biomedical Research, 280 Science 698 (1998) (citing Michael A. Heller, The Tragedy of the Anticommons: Property in the Transaction from Marx to Markets, 111 Harv. L. Rev. 621 (1998)).

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[24] The Human Genome Project was an international project initiated in 1990 with the aim of sequencing an entire human genome and in which Sir John Sulston, a Nobel laureate, actively participated. Sulston Decl. ¶¶, 22.

According to Dr. Fiona Murray ("Dr. Murray"), who received a grant to research the impact of gene patenting on scientific research and commercialization, 4382 of the 23,688 genes listed in the database of the National Center for Biotechnology Information ("NCBI") - nearly 20% of human genes - are explicitly claimed as United States intellectual property. Murray Decl. ¶ 6. After devising a study to gauge the impact of gene patenting on public knowledge that utilized the time lag between publication of papers on a gene sequence and the issuance of a patent claiming that gene sequence, Dr. Murray concluded that the Myriad patents have negatively impacted the public knowledge of the *BRCA1* and *BRCA2* genes by 5-10%. Murray Decl. ¶¶ 7-15, 20.

Plaintiffs have cited other studies to demonstrate the chilling effect of gene patents on the advancement of both genetic research and clinical testing. A survey of laboratory directors in the United States conducted by Dr. Mildred Cho (the "Cho study") found that 53% decided not to develop a new clinical test because of a gene patent or license, and 67% believed that gene patents decreased their ability to conduct research. Cho Decl. ¶ 10. This correlated with a study conducted by the American Society of Human Genetics that reported that 46% of respondents felt that patents had delayed or limited their research. Cho Decl. ¶ 11. The Cho study also revealed that of those who stopped performing a clinical test because of a gene patent or license, the largest number stopped doing *BRCA1* and *BRCA2* testing (with the same number having stopped Apolipoprotein E testing). Cho Decl. ¶ 16. Specifically, the survey found that nine labs had ceased performing *BRCA1/2* genetic testing as a result of the patents-in-suit. In addition to labs that have ceased performing *BRCAl/2* genetic testing, labs have avoided or refrained from developing tests for *BRCA1* and *BRCA2* as a result of the patents held by Myriad. Ostrer Decl. ¶ 6; Ledbetter Decl. ¶¶ 14-16. Studies of other gene patents have also revealed that labs frequently stop developing or offering clinical tests for disease as a result of gene patents. For example, a purportedly valid scientific survey of labs in the United States found a 26% drop in the number of labs performing testing for hemochromatosis as a result of gene patents. Cho Decl. ¶¶ 18-20.

Researchers, clinicians, and pathologists are aware that Myriad has sent cease and desist letters in connection with the patents-in-suit and that Myriad prohibits clinical testing of the *BRCA1/2* genes. Kazazian Decl. ¶¶ 5-11; Ganguly Decl. ¶¶ 4-14; Chung Decl. ¶ 15; Hegde Decl. ¶ 10; Matloff Decl. ¶¶ 5-7; Ostrer Decl. ¶¶ 4-7; Swisher Decl. ¶ 28; Hubbard Decl. ¶¶ 7-8; Kant Decl. ¶ 4; Ledbetter Decl. ¶ 13; Reich Decl. ¶¶ 3, 5; Parthasarathy Decl. ¶¶ 28-31. Myriad also does not permit researchers to tell patients involved in research the results of their *BRCA1/2* testing, leading physicians involved in breast cancer care and research unable to meet their ethical obligations to provide genetic test results to research subjects, when requested. Ostrer Decl. ¶ 10; Chung Decl. ¶ 13, 14. In addition to the direct benefits to the patient of knowing the results of their testing, such disclosure would also provide valuable insights into patient behavior that would enhance patient care. Ostrer Decl. ¶ 10. The AMA has also expressed its belief that the "[t]he use of patents . . . or other means to limit the availability of medical procedures places significant limitation on the dissemination of medical knowledge, and is therefore unethical." American Medical Association, Opinion 9.095 The Use of Patents and Other Means to Limit Availability of Medical Procedures, (adopted June 1995), available at http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion9095.html. In addition, others have argued that human genes are the common heritage of mankind whose use should not be restricted by patent grants. See, e.g., Pilar A.

Ossorio, The Human Genome as Common Heritage: Common Sense or Legal Nonsense?, 35 J.L. Med. & Ethics 425, 426 (2007); Melissa L. Sturges, Who Should Hold Property Rights to the Human Genome? An Application of the Common Heritage of Humankind, 13 Am. U. Int'l L. Rev. 219, 245 (1997); Barbara Looney, Should Genes Be Patented? The Gene Patenting Controversy: Ethical and Policy Foundations of an International Agreement, 26 Law & Pol'y Int'l Bus. 231 (1994); Hubert Curien, The Human Genome Project and Patents, 254 Science 1710, 1710-12 (1991).

According to Plaintiffs, Myriad has withheld critical data concerning genetic predisposition to breast cancer from the Breast Cancer Information Core ("BIC"), an international, open access online database that is a central repository for information about the *BRCA1/2* genes and their genetic variants. The BIC facilitates the identification of deleterious mutations (i.e. those associated with a higher risk of cancer), provides a mechanism to collect and distribute data about genetic variants, and plays an important role in helping to elucidate the significance of those variants through its collection of data. Swisher Decl. ¶¶ 15, 17, 18; Chung Decl. ¶ 22; Ostrer Decl. ¶ 13. Although the value of the BIC comes from the amount and quality of data provided by the scientific community, Myriad, according to Plaintiffs, has not contributed any data to BIC in the past two years. Sulston Decl. ¶ 36; Swisher Decl. ¶¶ 19-21; Ostrer Decl. ¶¶ 12-13; Chung Decl. ¶¶ 21-22; Ledbetter Decl. ¶ 20.

Plaintiffs also assert that gene patents impede the development of improved genetic testing. For example, as new sequencing technologies offer the possibility of faster and less expensive sequencing of a patient's genes, patents on one or more genes may impede scientists' ability to develop a comprehensive test for complex diseases or provide a person with an analysis of his or her entire genome. Sulston Decl. ¶ 38; Ledbetter Decl. ¶ 24. In addition, Plaintiffs assert that gene patents interfere with the ability of physicians and researchers to investigate complex diseases. For example, *BRCA1/2* may be associated with cancers other than breast and ovarian cancer, but so long as the patents on these genes remain, no one will be able to include these genes in tests for other disease predispositions. Ledbetter Decl. ¶¶ 24-25. Gene patents similarly impede the development and improvement of tests for diseases by geneticists. Ledbetter Decl. ¶¶ 14-15. Plaintiffs also assert that allowing only a single lab to offer testing means that the one lab dictates the standards for patient care in testing for that disease; in contrast, patient care is promoted when more than one lab offers a particular genetic test, utilizing different methodologies, since this can ensure the quality of the testing and accuracy of the test results. Chung Decl. ¶ 23; Ledbetter Decl. ¶ 23; Reich Decl. ¶¶ 9, 11; Ostrer Decl. ¶¶ 11; Parthasarathy Decl. ¶ 31.

Plaintiffs further assert that gene patents are not necessary to create incentives for initial discoveries or the development of commercial applications, including diagnostic tests. Cho Decl. ¶ 25; Leonard Decl. ¶¶ 20-21. Patents have not been necessary for the rapid introduction of genetic testing, as evidenced by genetic testing that has been offered prior to the issuance of a patent.

Cho Decl. ¶ 21. In support of this assertion, Plaintiffs cite a study of gene patents issued in the United States for genetic diagnostics that showed that 67% of these patents were issued for discoveries funded by the U.S. government. Cho Decl. ¶ 22. Similarly, another study showed that 63% of patents on gene sequences resulted from federally supported research. Leonard Decl. ¶ 22. As previously noted, the NIH provided $2 million in research grants to the University of Utah, or approximately one-third of the total funding, for the identification of the *BRCA1* sequence. Parthasarathy Decl. ¶ 18.

Myriad has contested these assertions and disputes the idea that patenting of isolated human DNA conflicts with the advancement of science. According to Myriad, the quid pro quo of the patent system is that inventors, in exchange for a limited period of patent exclusivity, must provide a sufficient description of the patented invention so that others may improve upon it. Reilly Decl. ¶ 24; Doll Decl. ¶ 44. Furthermore, according to Myriad, its policy and practice has been and still is to allow scientists to conduct research studies on *BRCA1* and *BRCA2* freely, the result of which has been the publication of over 5,600 research papers on *BRCA1* and over 3,000 research papers on *BRCA2,* representing the work of over 18,000 scientists. Critchfield Decl. ¶¶ 3, 13; Li Decl. ¶¶ 3-6; Baer Decl. ¶¶ 3-6; Parvin Decl. ¶¶ 3-6; Sandbach Decl. ¶¶ 3-7.

According to Myriad, patents on isolated DNA, including the patents-in-suit, actually promote research and advance clinical development to the benefit of patients. Reilly Decl. ¶¶38, 43: Critchfield

Decl. ¶¶ 2-18, 65, 68: Linck Decl. ¶¶ 27-28, 71, 73: Tavtigian Decl. ¶¶ 14-17; Doll Decl. ¶¶ 45-46; Schlessinger Decl. ¶¶ 31-32. Myriad has contended that gene patents are essential for obtaining capital investment in the development and commercialization of technological breakthroughs. Linck Decl. ¶¶ 27, 28; Reilly Decl. ¶¶ 16; Doll Decl. ¶ 46. In support, Myriad has cited a survey published in 2009 by the BIO of 150 biotechnology member companies in the therapeutic and diagnostic healthcare industry stating that the majority of companies (61%) generally in-licensed projects that are in the pre-clinical or Phase I stage of development, and thus still require substantial R&D investment and commercialization risk by the licensee. A substantial majority (77%) of the respondents without approved products indicated that they expect to spend 5-15 years and over $100 million developing a commercial product. Myriad asserts that these expenditures dwarf any initial research funding by the federal government. Reilly Decl. ¶ 22. In particular, Myriad notes that a significant amount of private investment led to its identification of the *BRCA1* and *BRCA2* sequences, with the expectation of patent protection providing an incentive to fund the research into the determination of the gene sequences. Skolnick Decl. ¶¶ 14-16. Therefore, Myriad asserts that absent the promise of a period of market exclusivity provided by patents and the infusion of venture and risk capital derived therefrom, companies such as Myriad that capitalize on innovation simply would not be created and their products would not be brought to market or the clinic. Reilly Decl. ¶¶18, 34, 51, 52, 62; Critchfield Decl. ¶¶ 67, 68; Linck Decl. ¶ 73.

Myriad also notes that it has made over 20,000 submissions to the BIC database, making it the largest contributor to the database. It has also published the largest clinical series of mutation risk in the *BRCA1/2* genes based on its testing data and has tabulated and posted the data on Myriad's website, where it is freely available to researchers throughout the world. Critchfield Decl. ¶¶ II, 12.

According to Myriad, the majority of academic researchers operating laboratories (as opposed to Clinical Laboratory Improvement Amendments ("CLIA")-certified laboratories) do not believe that they should share test results with subjects outside of the standard clinical setting. Reilly Decl. ¶ 57-59. As the declarations submitted by the parties make clear, there exists a sharp dispute concerning the impact of patents directed to isolated DNA on genetic research and consequently the health of society. As with the dispute concerning the effect of the patents-in-suit on *BRCA1/2* genetic testing, the resolution of these disputes of fact and policy are not possible within the context of these motions.

IV. THE PATENTS

A. Summary of the Patents

The subjects of this declaratory judgment action are fifteen claims contained in seven patents issued by the USPTO:[25] claims 1, 2, 5, 6, 7, and 20 of

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[25] The USPTO granted these patents pursuant to a formal written policy that permits the patenting of "isolated and purified" DNA encoding human genes and pursuant to a

U.S. patent 5,747,282 (the "'282 patent"); claims 1, 6, and 7 of U.S. patent 5,837,492 (the "'492 patent") ; claim 1 of U.S. patent 5,693,473 (the "'473 patent"); claim 1 of U.S. patent 5,709,999 (the "'999 patent"); claim 1 of U.S. patent 5,710,001 (the "'001 patent"); claim 1 of U.S. patent 5,753,441 (the "'441 patent"); and claims 1 and 2 of U.S. patent 6,033,857 (the "'857 patent").[26]

The claims-in-suit may be divided into two types of claims: composition claims and method, or process, claims. Independent claim 1 of the '282 patent representative of the group of composition claims and claims:

> An isolated DNA coding for a *BRCA1* polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO: 2.

This claim is therefore directed to an isolated DNA molecule possessing a nucleotide sequence that translates into the *BRCA1* protein. Because most amino acids can result from the translation of more than one DNA codon, multiple DNA sequences correspond to the nucleotide sequence claimed by this claim. Claim 2 of the '282 patent is dependent on claim 1 but contains an additional limitation that

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practice that permits such DNA patents and the patenting of correlations created by nature between natural elements of the body and a predisposition to disease. See Utility Examination Guidelines, 66 Fed. Reg. 1,093 (Jan. 5, 2001).

[26] For purposes of understanding what the claim terms would have meant to a person of ordinary skill in the art at the time of the application for the patents, an application date of August 1994 is presumed for the '282, '473, '999, '001, and '441 patents and December 1995 for the '492 and '857 patents.

identifies the specific *BRCA1* nucleotide sequence of the claimed DNA.[27] Claims 5 and 6 of the '282 patent are directed to fragments as short as 15 nucleotides of the DNA molecules claimed in claims 1 and 2 of the '282 patent.[28] Finally, claim 7 of the '282 patent and claim 1 of the '473 patent are directed to isolated DNA possessing one of the specified mutant *BRCA1* gene sequences.[29]

Claims 1, 6, and 7 of the '492 patent are also composition claims covering isolated DNA molecules containing certain specified nucleotide sequences relating to the *BRCA2* gene. Claim 1 is directed to an isolated DNA molecule encoding the BRCA2 protein.[30] Like claim 1 of the '282 patent, claim 1 of the '492 patent is directed to multiple possible DNA sequences as a result of the redundancy of the DNA codons. Claim 6 of the '492 patent, however, is considerably broader than claim 1 and is directed to any DNA nucleotide encoding any mutant *BRCA2* protein that is associated with a predisposition to breast cancer.[31] Claim 7 of the '492 patent depends on claim 6, but is restricted to the mutated forms of the *BRCA2* nucleotide sequence set forth in the specification.[32] As a result of the breadth of these composition claims, they reach isolated *BRCA1/2* DNA obtained from any human being.

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[27] Claim 2 of the '282 patent reads: "The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO: 1."

[28] Claim 5 of the '282 patent claims: "An isolated DNA having at least 15 nucleotides of the DNA of claim 1." Claim 6 of the '282 patent reads: "An isolated DNA having at least 15 nucleotides of the DNA of claim 2."

[29] Claim 7 of the '282 patent reads: "An isolated DNA selected from the group consisting of: (a) a DNA having the nucleotide sequence set forth in SEQ ID NO: 1 having T at nucleotide position 4056; (b) a DNA having the nucleotide sequence set forth in SEQ ID NO: 1 having an extra C at nucleotide position 5385; (c) a DNA having the nucleotide sequence set forth in SEQ ID NO: 1 having G at nucleotide position 5443; and (d) a DNA having the nucleotide sequence set forth in SEQ ID NO: 1 having 11 base pairs at nucleotide positions 189-199 deleted." Claim 1 of the '473 patent reads: "An isolated DNA comprising an altered BRCA1 DNA having at least one of the alterations set forth in Tables 12A, 14, 18 or 19 with the proviso that the alteration is not a deletion of four nucleotides corresponding to base numbers 4184-4187 in SEQ. ID. NO: 1."

Claim 1 of the '999 patent is representative of the group of method claims. It claims:

> A method for detecting a germline alteration in a *BRCA1* gene, said alteration selected from a group consisting of the alterations set forth in Tables 12A, 14, 18, or 19 in a human which comprises analyzing a sequence of a *BRCA1* gene or *BRCA1*

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[30] Claim 1 of the '492 patent reads: "An isolated DNA molecule coding for a BRCA2 polypeptide, said DNA molecule comprising a nucleic acid sequence encoding the amino acid sequence set forth in SEQ ID NO: 2."

[31] Claim 6 of the '492 patent reads: "An isolated DNA molecule coding for a mutated form of the BRCA2 polypeptide set forth in SEQ ID NO: 2, wherein said mutated form of the *BRCA2* polypeptide is associated with susceptibility to cancer."

[32] Claim 7 of the '492 patent reads: "The isolated DNA molecule of claim 6, wherein the DNA molecule comprises a mutated nucleotide sequence set forth in SEQ ID NO: 1. "

> RNA from a human sample or analyzing a sequence of *BRCA1* cDNA made from mRNA from said human sample with the proviso that said germline alteration is not a deletion of 4 nucleotides corresponding to base numbers 4184-4187 of SEQ ID NO: 1.

Thus, claim 1 of the '999 patent covers the process of identifying the existence of certain specific mutations in the *BRCA1* gene by "analyzing" the sequence of the *BRCA1* DNA, RNA, or cDNA made from *BRCA1* RNA obtained from a human sample.

Most of the remaining method claims-in-suit are similarly structured and directed to the comparison of gene sequences. Claim 1 of the '001 patent claims a method for determining whether a human tumor sample contains a mutation in the *BRCA1* gene by "comparing" the sequence of the *BRCA1* gene from the tumor with the sequence of the *BRCA1* gene from a non-tumor sample from the same person.[33] Claim 1 of the '441 patent and claim 1 of the '857 are both directed to the same process, differing only as to whether the claimed method is directed to *BRCA1* ('441) or *BRCA2* ('857). Both of these independent claims are directed to the process of determining whether an individual has inherited an altered *BRCA1* or *BRCA2* gene by "comparing" the individual's *BRCA1* or *BRCA2* gene sequence with the wild-type *BRCA1* or *BRCA2* gene sequence.[34] 34 Claim 2 of the '857 patent covers a method for determining whether an individual has a predisposition for breast cancer by "comparing" the individual's *BRCA2* gene sequence with the known wild-type *BRCA2* gene sequence.[35]

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[33] Claim 1 of the '001 patent reads "A method for screening a tumor sample from a human subject for a somatic alteration in a *BRCA1* gene in said tumor which comprises gene comparing a first sequence selected form [sic] the group consisting of a *BRCA1* gene from said tumor sample, *BRCA1* RNA from said tumor sample and *BRCA1* cDNA made from mRNA from said tumor sample with a second sequence selected from the group consisting of *BRCA1* gene from a nontumor sample of said subject, *BRCA1* RNA from said nontumor sample and *BRCAI* cDNA made from mRNA from said nontumor sample, wherein a difference in the sequence of the BRCAI gene, *BRCAI* RNA or *BRCA1* cDNA from said tumor sample from the sequence of the *BRCA1* gene, *BRCA1* RNA or *BRCA1* cDNA from said

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nontumor sample indicates a somatic alteration in the *BRCA1* gene in said tumor sample."

[34] Claim 1 of the '441 patent reads: "A method for screening germline of a human subject for an alteration of a *BRCA1* gene which comprises comparing germline sequence of a *BRCA1* gene or *BRCA1* RNA from a tissue sample from said subject or a sequence of BRCA1 cDNA made from mRNA from said sample with germline sequences of wild-type BRCAI gene, wild-type BRCAI RNA or wild-type *BRCA1* cDNA, wherein a difference in the sequence of the *BRCA1* gene, *BRCA1* RNA or *BRCA1* cDNA of the subject from wild-type indicates an alteration in the *BRCA1* gene in said subject." Claim I of the '857 patent claims: "A method for identifying a mutant *BRCA2* nucleotide sequence in a suspected mutant *BRCA2* allele which comprises comparing the nucleotide sequence of the suspected mutant *BRCA2* allele with the wild-type *BRCA2* nucleotide sequence, wherein a difference between the suspected mutant and the wild-type sequences identifies a mutant *BRCA2* nucleotide sequence."

[35] Claim 2 of the '857 patent reads: "A method for diagnosing a predisposition for breast cancer in a human subject which comprises comparing the germline sequence of the *BRCA2* gene or the sequence of its mRNA in a tissue sample from said subject with the germline sequence of the wild-type *BRCA2*

Finally, claim 20 of the '282 patent claims a method for determining the effectiveness of a potential cancer therapeutic comprising growing cells carrying an altered *BRCA1* gene known to cause cancer in the presence and absence of a potential cancer therapeutic, comparing the growth rates of the cells, and concluding that a slower growth rate in the presence of the potential therapeutic indicates that it is indeed a cancer therapeutic.[36]

B. Construction of the Claims[37]

1. Legal standard

Before considering the patent-eligibility of a patent claim, the disputed terms in the claims must

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gene or the sequence of its mRNA, wherein an alteration in the germline sequence of the *BRCA2* gene or the sequence of its mRNA of the subject indicates a predisposition to said cancer."

[36] Claim 20 of the '282 patent reads: "A method for screening potential cancer therapeutics which comprises: growing a transformed eukaryotic host cell containing an altered BRCAI gene causing cancer in the presence of a compound suspected of being a cancer therapeutic, growing said transformed eukaryotic host cell in the absence of said compound, determining the rate of growth of said host cell in the presence of said compound and the rate of growth of said host cell in the absence of said compound and comparing the growth rate of said host cells, wherein a slower rate of growth of said host cell in the presence of said compound is indicative of a cancer therapeutic."

[37] In addition to the claim terms discussed below, the parties also dispute the proper interpretation of the method claims i.e., whether they may be construed to encompass certain transformative steps. Because this issue is broader in scope than simple claim term definition, it is addressed *infra* in Section VII.D.

be construed in order ensure the scope of the claims is accurately assessed. See, e.g., Datamize, LLC v. Plumtree Software, Inc., 417 F.3d 1342, 1354 (Fed. Cir. 2005) ("[A] utility patent protects 'any new and useful process, machine, manufacture, or composition of matter, or any new or useful improvement thereof,' 35 U.S.C. § 101 (2000), the scope of which is defined by the patent's written claims."). Courts are charged with interpreting disputed claim terms as a matter of law. Markman v. Westview Instruments, Inc., 517 U.S. 370, 384-85 (1996).

In interpreting the meaning of claim terms, "words of a claim are generally given their ordinary and customary meaning" to a person of ordinary skill in the art at the time of invention (i.e., the effective filing date of the patent application). Philips v. AWH Corp., 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (internal citations and quotation marks omitted). "Importantly, the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." Id. at 1313. Thus, the Federal Circuit has emphasized the importance of "intrinsic" evidence in claim construction: the words of the claim themselves, the written description in the patent's specification, and, when necessary, the history of the patent application's prosecution before the USPTO. Id. at 1314-17.

The process of claim construction begins with the language of the claims themselves. The language of the claim is what the patentee chose to use to "'particularly point [ ] out and distinctly claim [ ] the subject matter which the applicant regards as his invention.'" Id. at 1311-12 (quoting 35 U.S.C. § 112, ¶ 2). Thus, "the claims themselves provide substantial guidance as to the meaning of particular claim terms." Id. at 1314. In addition to the particular claim being examined, the context provided by other claims may be helpful as well. "For example, the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim." Id. at 1314-15.

Claim language must also be read in the context of the specification. Id. at 1315. As the Federal Circuit has made clear, "claims, of course, do not stand alone. Rather, they are part of 'a fully integrated written instrument,' consisting principally of a specification that concludes with the claims." Id. (quoting Markman v. Westview Instruments, Inc., 52 F.3d 967, 978 (Fed. Cir. 1995). "For that reason, claims 'must be read in view of the specification, of which they are a part.'" Id. (quoting Markman, 52 F.3d at 979). The specification "is always highly relevant to the claim construction analysis. Usually it is dispositive; it is the single best guide to the meaning of a disputed term." Id. (quoting Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996)). Moreover, when the patentee "act[s] as his or her own lexicographer" and includes an explicit definition of a claim term in the specification, that definition is dispositive over any ordinary meaning. Id. at 1319 (internal citation and quotation marks omitted); see also Digital Biometrics, Inc. v. Identix, Inc., 149 F.3d 1335, 1344 (Fed. Cir. 1998).

In relying on the specification to interpret claim terms, the Federal Circuit has also "repeatedly warned against confining the claims" to the embodiments described in the specification. Phillips, 415 F.3d at 1323. The mistake of "reading a limitation from the written description into the claims" is one of the cardinal sins of patent law." Id. at 1320 (quoting SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc., 242 F.3d 1337, 1340 (Fed. Cir. 2001)).

Courts may also utilize the prosecution history which "consists of the complete record of the proceedings before the PTO and includes the prior art cited during the examination of the patent . . . . [T]he prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." Id. at 1317 (internal citations omitted). However, the prosecution history "often lacks the clarity of the specification and thus is less useful claim construction purposes." Id.

Lastly, courts may rely on extrinsic evidence such as dictionaries, treatises, and expert testimony, which may serve to provide a source of "accepted meaning of terms used in various fields of science and technology," or by providing "background on the technology at issue." Id. at 1317-18. However, such "extrinsic" evidence is "less significant than the intrinsic record in determining the legally operative meaning of the claim language." Id. At 1317 (internal citations and quotation marks omitted). The use of extrinsic evidence may not be used to contradict the meaning of the claim terms as evidenced by the intrinsic evidence. Id. at 1317-19; Biagro W. Sales, Inc. v. Grow More, Inc., 423 F.3d 1296, 1302 (Fed. Cir. 2005).

2. Resolution of the disputed claim terms

a. "DNA" and "isolated DNA"

The parties approach the terms "DNA" and "isolated DNA" from opposing perspectives.[38] Plaintiffs contend that the term "DNA" means "a sequence of nucleic acids, also referred to as nucleotides" and therefore constitutes a "nucleotide sequence" or a "polynucleotide," Pl. Br. at 10.[39] Myriad disputes Plaintiffs' definition of "DNA" insofar as Plaintiffs' definition suggests that the term "DNA" refers merely to information, that is, "a description of the linear order of nucleotide units that make up the polynucleotide." Myriad Br. at 15. Myriad instead argues that "DNA" refers to "a real and tangible molecule, a chemical composition made up of deoxyribonucleotides linked by a phosphodiester backbone." Myriad Br. at 14.

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[38] The degree to which the parties actually disagree on the meaning of the discussed claim terms is unclear; however, to the extent some disagreement has been noted by the parties, this section seeks to resolve them.

[39] For purposes of this opinion, "Pl. Br." refers to Plaintiffs' Memorandum of Law in Support of Motion for Summary Judgment; "Myriad Br." refers to Myriad Defendants' Memorandum of Law (1) in Support of Their Motion for Summary Judgment and (2) in Opposition to Plaintiffs' Motion for Summary Judgment; "Pl. Reply" refers to the Memorandum of Law (1) in Further Support of Plaintiffs' Motion for Summary Judgment Against All Defendants and (2) in Opposition to the Myriad Defendants' Motion for Summary Judgment and (3) in Opposition to Defendant United States Patent and Trademark Office's Motion for Judgment on the Pleadings; "Myriad Reply" refers to Myriad Defendants' Memorandum in Reply to Plaintiffs' Opposition to Myriad Defendants' Motion for Summary Judgment; and "USPTO Reply" refers to the Reply Memorandum of Law in Further Support of Defendant United States Patent and Trademark Office's Motion for Judgment on the Pleadings and in opposition to Plaintiffs' Motion for Summary Judgment.

As its name implies, DNA, or deoxyribonucleic acid, is an acid a tangible, chemical compound. As Myriad correctly notes, the specifications make clear that "DNA," as used in the patents, refers to the physical manifestation of the acid, one that may be "substantially separated from other cellular components which naturally accompany a gene." '473 patent, col. 19: 8-9; '282 patent, col. 19: 10-11; '492 patent, col. 17: 64-65. Despite the description of the term "DNA" set forth in the briefs, this understanding of the meaning of "DNA" is shared by both Plaintiffs' and Myriad's declarants. Kay ¶ 125; Linck ¶ 45; Schlessinger ¶ 12; Grody ¶ 10; Leonard ¶ 30.

The term "isolated DNA" is defined by Plaintiffs as "a fragment of DNA substantially separated from other cellular components and other DNA." Pl. Br. at 10. Myriad disputes Plaintiffs' definition insofar as it implies that fragments of DNA exist free-floating in the cell, separate from other cellular components, such as proteins and the other DNA in the chromosome. Myriad Br. at 16. The patent specifications expressly define "isolated DNA" as a DNA molecule "which is substantially separated from other cellular components which naturally accompany a native human sequence [such as] human genome sequences and proteins" and "includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems." '473 patent, col. 19: 6-15; '282 patent, col. 19: 8-18; '492 patent, col. 17: 62-18:5.

"Isolated DNA" is therefore construed to refer to a segment of DNA nucleotides existing separate from other cellular components normally associated with native DNA, including proteins and other DNA sequences comprising the remainder of the genome, and includes both DNA originating from a cell as well as DNA synthesized through chemical or heterologous biological means.

b. "BRCA1" and "BRCA2 "

Plaintiffs define the term "BRCA1" as "a particular fragment of DNA found on chromosome 17 that relates to a person's predisposition to develop breast and ovarian cancer." Pl. Br. at 11. Similarly, Plaintiffs define the term "BRCA2" as "a particular fragment of DNA found on chromosome 13 that relates) to a person's predisposition to develop breast and ovarian cancer." Pl. Br. at 14. As with Plaintiffs' proposed definition of "isolated DNA," Myriad argues that these definitions are inconsistent with the patents' definition of "BRCA1" and "BRCA2" as "cancer-predisposing gene[sl. some alleles of which cause susceptibility to breast and ovarian cancers" because they suggest that the *BRCA1* and *BRCA2* genes are not integrated into a chromosome, but are broken, detached, or otherwise easily removed from their respective chromosomes. Myriad Br. at 16.

The specifications of the patents-in-suit define the terms "BRCAI" and "BRCA2" as "a human breast cancer predisposing gene . . . some alleles of which cause susceptibility to cancer, in particular breast and ovarian cancer." '282 patent, col. 4:33-36; see also '282 patent, col. 1: 22-23; '492 patent, col. 1: 20-21, 4:28-29. Further, neither party disputes that "genes" refer to segments of DNA incorporated into chromosomes.

"BRCA1" is therefore construed to refer to a human gene, normally integrated into chromosome 17, some alleles of which cause susceptibility to breast and ovarian cancer. Similarly, "BRCA2" is construed to refer to a human gene, normally integrated into chromosome 13, some alleles of which cause susceptibility to breast and ovarian cancer.

V. CONCLUSIONS OF LAW

A. The Summary Judgment Standard

Summary judgment is granted only where there exists no genuine issue of material fact and the moving party is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(c); see Celotex Corp. v. Catrett, 477 U.S. 317, 322 3 (1986); SCS Commc'ns, Inc. v. Herrick Co., 360 F.3d 329, 338 (2d Cir. 2004). The courts do not try issues of fact on a motion for summary judgment, but, rather, determine "whether the evidence presents a sufficient disagreement to require submission to a jury or whether it is so one-sided that one party must prevail as a matter of law." Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 251-52 (1986).

"The party seeking summary judgment bears the burden of establishing that no genuine issue of material fact exists and that the undisputed facts establish [its] right to judgment as a matter of law."

Rodriguez v. City of New York, 72 F.3d 1051, 1060-61 (2d Cir. 1995). In determining whether a genuine issue of material fact exists, a court must resolve all ambiguities and draw all reasonable inferences against the moving party. See Matsushita Elec. Indus. CO. V. Zenith Radio Corp., 475 U.S. 574, 587-88 (1986); Gibbs-Alfano v. Burton, 281 F.3d 12, 18 (2d Cir. 2002). However, "the non-moving party may not rely simply on conclusory allegations or speculation to avoid summary judgment, but instead must offer evidence to show that its version of the events is not wholly fanciful." Morris v. Lindau, 196 F.3d 102, 109 (2d Cir. 1999) (internal quotation marks omitted).

Summary judgment is appropriate where the moving party has shown that "little or no evidence may be found in support of the nonmoving party's case. When no rational jury could find in favor of the nonmoving party because the evidence to support its case is so slight, there is no genuine issue of material fact and a grant of summary judgment is proper." Gallo v. Prudential Residential Servs., L.P., 22 F.3d 1219, 1223-24 (2d Cir. 1994) (internal citations omitted).

B. 35 U.S.C. § 101 and Its Scope

Section 101 of Title 35, United States Code, provides:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the

> conditions and requirements of this title.

In interpreting this language, the Supreme Court has observed that "Congress plainly contemplated that the patent laws would be given wide scope." Diamond v. Chakrabarty, 447 U.S. 303, 308 (1980); see also J.E.M. Ag Supply, Inc. v. Pioneer Hi:-Bred Int'l, Inc., 534 U.S. 124, 131 (2001) ("[W]e are mindful that this Court has already spoken clearly concerning the broad scope and applicability of § 101.")

However, this broad reading of § 101 and statutory patent eligibility is not without limits. "The Supreme Court has recognized that scientific principles and laws of nature, even when for the first time discovered, have existed throughout time, define the relationship of man to his environment, and, as a consequence, ought not to be the subject of exclusive rights to anyone person." In re Meyer, 688 F.2d 789, 795 (C.C.P.A. 1982) (citing Leroy v. Tatham, 55 U.S. 155, 175 (1852)). Specifically, the Supreme Court has recognized three categories of subject matter that fall outside the scope of § 101: "The laws of nature, physical phenomena, and abstract ideas have been held not patentable." Chakrabarty, 447 U.S. at 309; see also Diamond v. Diehr, 450 U.S. 175, 185 (1981). "The rule that the discovery of a law of nature cannot be patented rests, not on the notion that natural phenomena are not processes, but rather on the more fundamental understanding that they are not the kind of 'discovery' that the statute was enacted to protect." Parker v. Flook, 437 U.S. 584, 593 (1978).

The exclusion of products of nature[40] as patentable subject matter under § 101 also reflects the Supreme Court's recognition that "[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." Gottschalk v. Benson, 409 U.S. 63, 67 (1972). Thus, as Justice Breyer has observed, "the reason for this exclusion is that sometimes *too much* patent protection can impede rather than 'promote the Progress of Science and useful Arts,' the constitutional objective of patent and copyright protection." Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc., 548 U.S. 124, 126-27 (2006) (Breyer, *J.*, dissenting) (quoting U. S. Const., Art. I, § 8, cl. 8.) (emphasis in original). For these reasons, "manifestations of laws of nature [are] free to all men and reserved exclusively to none." Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 130 (1948).

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[40] Myriad distinguishes between "laws of nature," "natural phenomena," and "abstract ideas." which it concedes are not patentable, and "products of nature," for which it appears to argue no prohibition to patentability exists. Although the distinction between these two categories is unclear, it is well established that "products of nature" are not patentable. See, e.g., Chakrabarty, 447 U.S. at 13 (stating that relevant distinction for § 101 patentability is "between products of nature, whether living or not, and human-made inventions"); Gen. Elec. Co. *v.* De Forest Radio Co., 28 F.2d 641, 642 (3d Cir. 1928) (noting that "a patent cannot be awarded for a discovery or for a product of nature, or for a chemical element"); In re Marden, 47 F.2d 957, 957 (C.C.P.A. 1931) (concluding that "[u]ranium is a product of nature, and the appellant is not entitled to a patent on the same, or upon any of the inherent natural qualities of that metal"); In re Marden, 47 F.2d 958, 959 (C.C.P.A. 1931) (stating that "pure vanadium is not new in the inventive sense, and, it being a product of nature, no one is entitled to a monopoly of the same").

The inquiry into an invention's patent eligibility is a fundamental one, and as such, "[t]he obligation to determine what type of discovery is sought to be patented must precede the determination of whether that discovery is, in fact, new or obvious." Flook, 437 U.S. at 593; see also In re Bilski, 545 F.3d 943, 950 (Fed. Cir. 2008) (en banc), cert. granted, 129 S. Ct. 2735 (2009) ("Whether a claim is drawn to patent-eligible subject matter under § 101 is a threshold inquiry, and any claim of an application failing the requirements of § 101 must be rejected even if it meets all of the other legal requirements of patentability." (citing In re Comiskey, 499 F.3d 1365, 1372 (Fed. Cir. 2007)); Prometheus Labs. v. Mayo Collaborative Servs., 581 F.3d 1336, 1343 (Fed. Cir. 2009) (noting that in determining patent eligibility, "it is improper to consider whether a claimed element or step in a process is novel or nonobvious, since such considerations are separate requirements set forth in 35 U.S.C. §§ 102, and 103, respectively." (citing Bilski, 545 F.3d at 958)). Consistent with this approach, the courts have rejected patent claims even when the purported invention was highly beneficial or novel, or the research and work that went into identifying it was costly or time-consuming. See, e.g., Funk Bros., 333 U.S. at 130; Am. Fruit Growers, Inc. v. Brodgex Co., 283 U.S. 1, 11-13 (1931); Gen. Elec. Co. v. De Forest Radio Co., 28 F.2d 641, 642-43 (3d Cir. 1928).

The distinction between the § 101 inquiry into patentable subject matter and the other requirements for patentability set forth in Title 35 is of particular importance in evaluating the authorities cited by the parties and the arguments presented. The discussion of § 101 in In re Bergy, 596 F.2d 952 (C.C.P.A. 1979) by the late Honorable Giles S. Rich, one of the authors of the 1952 Patent Act, is particularly informative in clarifying the proper scope of a § 101 analysis. There, Judge Rich stated what considerations were salient - and importantly, what considerations were not - in a § 101 analysis:

> Section 101 states three requirements: novelty, utility, and statutory subject matter. The understanding that these three requirements are separate and distinct is long-standing and has been universally accepted. • . . Thus, the questions of whether a particular invention is novel or useful are questions wholly apart from whether the invention falls into a category of statutory subject matter. *Of the three requirements stated in § 101, only two, utility and statutory subject matter, are applied under § 101.* As we shall show, in 1952 Congress voiced its intent to consider the novelty of an invention under § 102 where it is first made clear what the statute means by "new," notwithstanding the fact that this requirement is first named in § 101.

Id. at 960-61 (emphasis added). Judge Rich further cautioned that "statements in the older cases must be handled with care lest the terms used in their reasoning clash with the reformed terminology of the present statute; lack of meticulous care may lead to distorted legal conclusions." Id. at 959. The Supreme Court subsequently affirmed this understanding of the § 101 analysis in Diehr, noting that while it had been argued that "novelty is an appropriate consideration under § 101," "[t]he question . . . of whether a particular invention is novel is 'wholly a part from whether from whether the invention falls into a category of statutory subject matter.'" 450 U.S. at 189-90 (quoting Bergy, 596 F.2d at 961); see also Bilski, 545 F.3d at 958 ("So here, it is irrelevant to the § 101 analysis whether Applicants' claimed process is novel or nonobvious.")

Accordingly, in considering whether the patents-in-suit comply with § 101, the proper analysis requires determining (1) whether the claimed invention possesses utility; and (2) whether the claimed invention constitutes statutory subject matter, that is, whether it is a "process, machine, manufacture, or composition of matter, or any new and useful improvement thereof," 35 U.S.C. § 101, or whether the claimed invention instead falls within the judicially created "products of nature" exception to patentable subject matter, i.e., "laws of nature, natural phenomenon, and abstract ideas," Chakrabarty, 447 U.S. at 309. In contrast, the question of whether an invention is "new" or "novel" over the prior art is a question addressed by § 102 and falls outside of the scope of the present § 101 analysis. Because it is undisputed that the claimed compositions and methods possess utility, the sole task of this Court is to resolve whether the claimed compositions and methods constitute statutory subject matter or fall within the judicially created products of nature exception to patentable subject matter.

C. The Composition Claims Are Invalid Under 35 U.S.C. § 101

As noted, the issue presented by the instant motions with respect to the composition claims is whether or not claims directed to isolated DNA containing naturally-occurring sequences fall within the products of nature exception to § 101. Based upon the reasons set forth below, it is concluded that the composition claims-in-suit are excepted.

1. Consideration of the Merits of Plaintiffs' Challenge is Appropriate

Myriad offers several arguments for why this Court should not engage the substance of Plaintiffs' claims, but should instead dismiss them out of hand. Foremost among them is Myriad's assertion that Plaintiffs' claims should be dismissed in light of the "carefully considered policy of the USPTO," which is "entitled to great respect from the courts." Myriad Br. at 26. In so arguing, Myriad notes the presumption of validity afforded to patents, see 35 U.S.C. § 282, and the USPTO's prior consideration of the eligibility of gene-related patents, see Utility Examination Guidelines 66 Fed. Reg. 1092, 1092-99 (Jan. 5, 2001), as well as the Supreme Court's statements in J.E.M. Ag Supply, 534 U.S. 124.

The Federal Circuit has previously held that it owes no deference to USPTO legal determinations. See, e.g., Arnold P'ship v. Dudas, 362 F.3d 1338, 1340 (Fed. Cir. 2004) '"This court reviews statutory interpretation, the central issue in this case, without deference."). While Congress has created a presumption of validity for issued patents, approximately 40% of patents challenged in the courts have been found invalid, demonstrating that this presumption is far from absolute. See Institute for Intellectual Property & Information Law, University of Houston Law Center, Patstats.org, Full Calendar Year 2008 Report, http://www.patstats.org/2008_Full_Year_Posting.rev3.htm (indicating that 40% of all validity determinations in federal court in 2008 found the challenged patent invalid); Paul F. Morgan & Bruce Stoner, Reexamination v. Litigation - Making Intelligent Decisions in Challenging Patent Validity, 86 J. Pat. & Trademark Off. Soc'y 441-461 (2004) (citing USPTO statistics showing that 74% of patents previously issued by the Patent Office and later challenged through the reexamination process were either canceled or changed by the USPTO). Moreover, the lack of Congressional action to specifically prohibit gene patents in response to the USPTO's prior grant of such patents does not preclude their review by the courts. For example, in Bilski, 545 F.3d 943, the Federal Circuit set out a test for the patentability of method claims that potentially will invalidate thousands of patents on business method patents, despite Congress' silence concerning the patentability of such methods. Finally, while the Supreme Court in J.E.M. Ag Supply noted the USPTO's practice of issuing patents on sexually reproducing plants in concluding that such plants represented patentable subject matter under § 101, that passing observation was neither dispositive nor central to the Court's holding and does not establish a rule of judicial deference to the USPTO's practices. See J.E.M. Ag Supply, 534 U.S. at 144-45. Indeed, the judicial deference urged by Myriad is difficult to reconcile with the courts' consideration of the substantive issues presented in cases such as Chakrabarty and indeed, J.E.M. Ag Supply itself.

Moreover, in the absence of a § 101 challenge to patent validity, the fact that courts have previously upheld the validity of patents directed to biological products in response to § 102 and/or § 103 challenges has no bearing on the present inquiry. See, e.g., In re Kubin, 561 F.3d 1351 (Fed. Cir. 2009) (considering obviousness of claims); In re O'Farrell, 853 F.2d 894 (Fed. Cir. 1988) (same). The Patent Act sets out patent invalidity as an issue to be raised by the parties, see 35 U.S.C. § 282, and it would be erroneous to treat a case involving DNA-related patents as holding that isolated human genes constitute patentable subject matter under § 101. Were that the case, the Supreme Court could have proceeded with its consideration of Metabolite Labs., after it granted certiorari and the parties and amici had fully briefed the issue of patentable subject matter eligibility, rather than dismissing certiorari as improvidently granted based on the parties' failure to raise the § 101 issue below. 548 U.S. 124.

Finally, Myriad's suggestion that invalidating the patents-in-suit would constitute an unconstitutional taking in violation of the Fifth Amendment of the Constitution or a violation of the United States' obligations under the Agreement on Trade-Related Aspects of Intellectual Property Rights ("TRIPS") is unpersuasive. Myriad's novel takings argument runs counter to a long history of invalidation of patent claims by the courts and is unsupported by legal precedent. Similarly, Articles 8.1 and 27.3 of TRIPS permit governments to incorporate public health concerns into their intellectual property laws and to exclude from patentability diagnostic, therapeutic, or surgical methods as well as particular inventions on the grounds of public interest. As a result, invalidation of the patents-in-suit would constitute neither a constitutional violation nor a conflict with the United States' treaty obligations.

2. Patentable subject matter must be "markedly different" from a product of nature

Supreme Court precedent has established that products of nature do not constitute patentable subject matter absent a change that results in the creation of a fundamentally new product. In American Fruit Growers, the Supreme Court rejected patent claims covering fruit whose skin had been treated with mold-resistant borax. Acknowledging that the "complete article is not found in nature," and "treatment, labor and manipulation" went into producing the fruit, the Court nonetheless held that the fruit did not become an "article of manufacture" unless it "possesses a new or distinctive form, quality, or property" compared to the naturally-occurring article.[41] 283 U.S. at 11. The Court went on to observe:

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[41] Myriad argues that American Fruit Growers was decided on novelty grounds, rather than subject matter patentability. See

> Manufacture implies a change, but every change is not manufacture, and yet every change in an article is the result of treatment, labor, and manipulation. But something more is necessary . . . There must be transformation; a new and different article must emerge having a distinctive name, character, or use.

Id. at 12-13 (quoting Anheuser-Busch Brewing Ass'n v. United States, 207 U.S. 556, 562 (1908)) (internal citation and quotation marks omitted).

Similarly, in Funk Brothers, the Supreme Court considered whether a mixture of several naturally-occurring species of bacteria was patentable.[42] 333 U.S. at 128-31. Each species of

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Myriad Br. at 26. However, the Court's novelty discussion was restricted to its analysis of the process claims. Am. Fruit Growers, 263 U.S. at 13-14 ("If it be assumed that the process claims under consideration cover an invention, we think this lacked novelty when application was made for the patent August 13, 1923"). In contrast, its rejection of the composition claims was based on an analysis of subject matter patentability. See id. at 11 ("Is an orange, the rind of which has become impregnated with borax, through immersion in a solution, and thereby resistant to blue mold decay, a 'manufacture,' or manufactured article, within the meaning of section 31, title 35, U.S. Code?").

[42] Myriad suggests that the Supreme Court's holding in Funk Brothers was premised on an obviousness determination, rather than patentable subject matter. Subsequent Supreme Court opinions, however, have treated the holding in Funk Brothers as a statement of patentable subject matter. See Chakrabarty, 447 U.S. at 309-10; Flook, 437 U.S. at 591-92; Benson, 409 U.S. at 67-68.

bacteria in the mixture could extract nitrogen from the air for plant usage. While the patent holder had created a mixture by selecting and testing for strains of bacteria that did not mutually inhibit one another, the Court concluded that the patent holder "did not create a state of inhibition or of non-inhibition in the bacteria. Their qualities are the work of nature. Those qualities are of course not patentable." Id. at 130.

Most recently, the Supreme Court addressed the application of § 101 to product claims in Diamond v. Chakrabarty, 447 U.S. 303. In Chakrabarty, the Court considered whether a "live, human-made micro-organism is patentable subject matter under 35 U.S.C. I 101." Id. At 305. The microorganism in question was a bacterium that had been genetically engineered to break down multiple components of crude oil and possessed considerable utility in the treatment of oil spills. Id. In concluding that the man-made bacterial strain was patentable, the Court observed that the claim "is not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter - a product of human ingenuity 'having a distinctive name, character [and] use.'" Id. at 309-10 (quoting Hartranft v. Wiegmann, 121 U.S. 609, 615 (1887)). The Court went on to contrast the Chakrabarty bacterium with the bacterial mixture at issue in Funk Brothers, stating that in Chakrabarty's case, "the patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility. His discovery is not nature's handiwork, but his own

. . . ." Id. at 310.[43] This requirement that an invention possess "markedly different characteristics" for purposes of § 101 reflects the oft-repeated requirement that an invention have "a new or distinctive form, quality, or property" from a product of nature. Am. Fruit Growers, 283 U.S. at 11; In re Merz, 97 F.2d 599,601 (C.C.P.A. 1935) ("[M]ere purification of known materials does not result in a patentable product," unless "the product obtained in such a case had properties and characteristics which were different in kind from those of the known product rather than in degree.").

Courts have also specifically held that "purification" of a natural compound, without more, is insufficient to render a product of nature patentable. In The American Wood-Paper Co. v. The Fibre Disintegrating Co., 90 U.S. (23 Wall.) 566 (1874), the Supreme Court held that refined cellulose, consisting of purified pulp derived from wood and vegetable, was unpatentable because it was "an extract obtained by the decomposition or disintegration of material substance." Id. at 593. As the Court observed:

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[43] Although Chakrabarty is often cited for the proposition that "anything under the sun that is made by man" is patentable, id. at 309, that phrase is a misleading quotation from the legislative history of the Patent Act of 1952. The full quote clearly acknowledges the statutory limitations to patentable subject matter: "A person may have 'invented' a machine or a manufacture, which may include anything under the sun made by man, but it is not necessarily patentable under section 101 unless the conditions of the title are fulfilled." H.R. Rep. No. 1923. 82d Cong., 2d Sess. 6 (1952).

> There are many things well known and valuable in medicine or in the arts which may be extracted from divers[e] substances. But the extract is the same, no matter from what it has been taken. A process to obtain it from a subject from which it has never been taken may be the creature of invention, but the thing itself when obtained cannot be called a new manufacture.

Id. at 593-94.[44] Similarly, in Cochrane v. Badische Anilin & Soda Fabrik, 111 U.S. 293 (1884), the Court rejected a patent on an artificial version of a natural red dye called alizarine that was produced by manipulating another compound through acid, heat, water or distillation. See generally, id. Although the artificial version of the dye was of a brighter hue than the naturally occurring dye, the Court concluded that "[c]alling it artificial alizarine did not make it a new composition of matter, and patentable as such . . . ." Id. at 311 (citing Am. Wood-Paper, 90 U.S. (23 Wall.) at 593).

In General Electric, 28 F.2d at 642, the Third Circuit Court of Appeals considered the patentability of purified tungsten, which possessed superior characteristics and utility over its brittle, naturally-occurring form. The court first noted that "[i]f it is a natural thing then clearly, even if [the patentee] was the first to uncover it and bring it into view, he cannot have a patent for it because a patent cannot be awarded for a discovery or for a product of nature, or for a chemical element." Id. The court went on to state:

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[44] Given the posture of the challenge to the patent's validity, the Court rested its holding on the fact that the patent in question was invalid as non-novel. Id.

> Naturally we inquire who created pure tungsten. Coolidge? No. It existed in nature and doubtless has existed there for centuries. The fact that no one before Coolidge found it there does not negative its origin or existence.
>
> The second part of the claim reads: "Having ductility and high tensile strength." Did Coolidge give those qualities to "substantially pure tungsten"? We think not for it is now conceded that tungsten pure is ductile cold. If it possess that quality now it is certain that it possessed it always.

Id. at 643. The Court of Customs and Patent Appeals ("C.C.P.A."), the precursor to the Federal Circuit Court of Appeals,[45] subsequently relied on General Electric in rejecting patents claiming purified uranium and vanadium. See In re Marden, 47 F.2d 957, 957-58 (C.C.P.A. 1931) ("Marden I"); In re Marden, 47 F.2d 958, 1059 (C.C.P.A. 1931) ("Marden II") ("The quality of purity of vanadium or its ductility is a quality of a natural product and as such is not patentable."). Similarly, in Ex Parte Latimer, the Patent Commissioner refused to allow a patent on pine needle fibers that were better suited for textile production, even though it was necessary to remove the needle from its sheath and other resinous material. 1889 Dec. Comm'r Pat. 123, 125 (1889) ("Nature made them so and not the process by which they are taken from the leaf or needle.").

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[45] The decisions of the C.C.P.A. remain binding precedent in patent cases. See South Corp. v. United States, 690 F.2d 1368, 1370-71 (Fed. Cir. 1982) (en banc) (adopting "([t]hat body of law represented by the holdings of . . the Court of Customs and Patent Appeals" as "precedent" for the then-new Federal Circuit so as to "continu[e] the stability in those areas of the law previously within the jurisdiction of our predecessor courts").

Myriad argues that purification of "'naturally occurring' compounds that 'do not exist in nature in pure form' renders such compounds patent-eligible." Myriad Br. at 21 (quoting In re Bergstrom, 427 F.2d 1394, 1401 (C.C.P.A. 1970)). However, Myriad cites no Supreme Court authority that would rebut the authorities presented by Plaintiffs, nor do the cited cases support Myriad's position.

Myriad has relied heavily on the holding of the Honorable Learned Hand in Parke-Davis & Co. v. H.K. Mulford Co., 189 F.2d 95 (S.D.N.Y. 1911).[46] In

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[46] The invocation of Judge Hand is frequently practiced in this Circuit. See, e.g., United States v. Rigas, 583 F.3d 108, 121 n.3 (2d Cir. 2009) (quoting Learned Hand for the proposition that appellate courts may not *find facts*); United States v. Parker, 554 F.3d 230 (2d Cir. 2009) (quoting Learned Hand for his formulation of the requirements of conspiracy); In re City of New York, 522 F.3d 279, 284 (2d Cir. 2008) (citing Learned Hand for his formulation of negligence); In re Hyman, 501 F.3d 61, 67 (2d Cir. 2007) (quoting at length Learned Hand's inconclusive discussion of the meaning of the word "defalcation"

Parke-Davis, Judge Hand considered a challenge to the validity of a patent claiming an adrenaline compound that had been isolated and purified from animal suprarenal glands. Id. at 97. It had been known that suprarenal glands in powdered form had hemostatic, blood-pressure-raising and astringent properties, but could not be used for those purposes

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in 11 U.S.C. § 523 (a) (4)); United States v. Brand, 467 F.3d 179, 190 (2d Cir. 2006) (quoting Learned Hand's definition of inducement by the government); In re Enron Corp., 419 F.3d 115, 123 (2d Cir. 2005) (quoting Learned Hand's critique of statutes of limitations); Shannon v. Jacobowitz, 394 F.3d 90, 95 (2d Cir. 2005) (quoting Learned Hand's instruction that "[w]ords are not pebbles in alien juxtaposition . . . "); Danahy v. Buscaglia, 134 F.3d 1185, 1189 (2d Cir. 1998) (quoting Learned Hand on the rationale for qualified immunity). See also, Remarks .of the Honorable John M. Walker, Jr. Upon Receiving the Learned Hand Medal for Excellence in Federal Jurisprudence, 76 St. John's L. Rev. 595, 596 (2002) ("Judge Hand is widely considered to have been one of the four greatest judges of the first half of the twentieth century."); James L. Oakes, Personal Reflections on Learned Hand and the Second Circuit, 47 Stan. L. Rev. 387 (1995); Gerald Gunther, Learned Hand: the Man and the Judge (1994): Kathryn Griffin, Judge Learned Hand and the Role of the Federal Judiciary (1973); Marvin Schick, Learned Hand's Court (1970); Marcia Nelson, ed., The Remarkable Hands: An Affectionate Portrait (1983): Hershel Shanks, ed., The Art and Craft of Judging: The Decisions of Judge Learned Hand (1968). Although Judge Hand once turned his back on the author of this opinion arguing before him on behalf of the Government, his opinion in Parke-Davis deserves careful review but brings to mind that oft repeated adage "*Quote Learned, but follow Gus.*" See Oakes, 47 Stan. L. Rev. at 389 n.175. This author, confronted by genomics and molecular biology, also emphatically empathizes with Judge Hand's complaint in Parke-Davis about his lack of knowledge of the rudiments of chemistry. See Parke-Davis, 189 F. at 114.

in gross form. The isolated adrenaline, however, possessed the desired therapeutic properties and could be administered to humans.

Although Myriad argues that the holding in Parke-Davis establishes that the purification of a natural product necessarily renders it patentable, the opinion, read closely, fails to support such a conclusion. The question before the court in Parke-Davis was one of novelty (a modern-day § 102 question), not of patentable subject matter (the § 101 question before this Court). In framing the issue, Judge Hand observed that, "[the validity of the claims] is attacked, first, because they are *anticipated* in the art; and second, for a number of technical grounds which I shall take up in turn." Id. at 101 (emphasis added). He went on to conclude that the patented purified extract was not, in fact, different from the prior art "only for a degree of purity," but rather was a different chemical substance from that found in the prior art. Id. at 103 (observing that "no one had ever isolated a substance [adrenaline] which was not in salt form" and that "the [claimed] base [form of adrenaline] was an original production of [the patentee's]"). Thus, Judge Hand held that the purified adrenaline was not anticipated by the prior art, namely, the ground paradrenal gland that was known to possess certain beneficial properties. See Merck & Co. v. Olin Mathieson Chem. Corp., 253 F.2d 156, 162 (4th Cir. 1958) ("It was further held [in Parke-Davis] that the invention was not anticipated, though the principle was known to exist in the suprarenal glands.").

Only after concluding that the claimed purified adrenaline was novel over the prior art did

Judge Hand offer, as dicta, the statement to which Myriad cites: "But, even if it were merely an extracted product without change, there is no rule that such products are not patentable." Id. at 103. While the accuracy of this statement at the time was written is dubious in light of American Wood-Paper (to which Judge Hand did not cite) it is certainly no longer good law in light of subsequent Supreme Court cases, which, as noted above, require that a claimed invention possess "markedly different characteristics" over products existing in nature in order for it to constitute patentable subject matter.[47] Chakrabarty, 447 U.S. at 310; see also Funk Bros., 333 U.S. at 130-32. By the same token, Judge Hand's suggestion that a claimed invention was patentable since it was a "new thing commercially and therapeutically," Parke-Davis, 189 F.2d at 103, is firmly contradicted by subsequent case law establishing that "it is improper to consider whether a claimed element or step in a process is novel or nonobvious, since such considerations are separate requirements" when evaluating whether a claim is patent-eligible subject matter. Prometheus, 581 F.3d at 1343; see also Bergy, 596 F.2d at 960-61. Such an approach would also be inconsistent with the Supreme Court's rejection of the patentability the commercially useful mixture of bacteria in Funk Brothers, the refined cellulose in American Wood-Paper, and the electromagnetic communication devices in O'Reilly v. Morse, 56 U.S. (15 How.) 62 (1853).

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[47] Notwithstanding Judge Hand's reputation, see supra note 46, his opinion in Parke-Davis was one of a district court judge and does not supersede contrary statements of the law by the C.C.P.A. or the Supreme Court.

The distinction between considerations of novelty and patentable subject matter similarly undermines Myriad's reliance on Bergstrom and In re Kratz, 592 F.2d 1169 (C.C.P.A. 1979), both of which presented issues of novelty and anticipation rather than the question of patentable subject matter. In Bergstrom, the C.C.P.A. considered an appeal from a rejection by the Board of Patent and Interferences ("BPAI") of a patent claiming the purified prostaglandins PGE_2 and PGE_3 that had been extracted from human or animal prostate glands. 427 F.2d at 1398. Although the BPAI cited § 101 in its rejection, the C.C.P.A. recognized the issue as a § 102 question of novelty. Id. at 1400 ("Tested by the conventional evidentiary criteria or 'conditions for patentability' relevant to the present factual situation which Congress has expressed in the various provisions of 35 U.S.C. § 102, appellants are undoubtedly correct, for the Patent Office has not been able to . . . establish that the claimed subject matter lacks 'novelty.'"); see also id. at 1401 ("[T]he fundamental error in the board's position, as we see it, is the analysis and answer it gave to the sole issue it accurately posed whether the claimed pure materials are novel as compared with the less pure materials of the reference." (internal citation and quotation marks omitted)). Indeed, the C.C.P.A. itself has subsequently recognized that Bergstrom is properly viewed as a case concerning novelty. Bergy, 596 F.2d at 961 ("Our research has disclosed only two instances in which rejections for lack of novelty were made by the PTO under § 101 . . . In In re Bergstrom we in effect treated the rejection as if it had been made under § 102, observing in the process that 'The word "new" in § 101 is defined and to be construed in accordance with the provisions of § 102.'" (internal citation omitted)).

Kratz examined the rejection of a patent claiming a substantially purified chemical compound naturally occurring in strawberries, called 2-methyl-2-pentenoic acid ("2M2PA"). 592 F.2d at 1170. The patentee had appealed from the BPAI's determination that the purified compound was obvious over the prior art under § 103. See id. Although there was some discussion about whether the composition claimed was a naturally-occurring compound, the C.C.P.A. did not view the question before it as a § 101 inquiry. Instead, the court treated the appeal as a question of novelty and anticipation pursuant to § 102.[48] See, e.g., id. at 1174 ("It should be clear that an anticipation rejection in such a case is necessarily based on a dual footing.").[49]

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[48] The differences between the test applied in Kratz and the "markedly different" requirement set forth in Chakrabarty and other Supreme Court precedent further demonstrates that the Kratz court was engaged in a § 102 anticipation analysis and not a § 101 statutory subject matter analysis. See id. at 1174 (requiring, for a finding of anticipation, that "the natural composition must inherently contain the naturally occurring compound" and that "the claim must be of sufficient breadth to encompass both the known natural composition and the naturally occurring compound.").

[49] Bergy also cited by Myriad, considered the question of whether microorganisms constituted patentable subject matter, an issue subsequently addressed by the Supreme Court in Chakrabarty. It *did* not address the patentability of purified natural products, and its citation to Merck and Parke-Davis was only for the purpose of noting that courts had upheld

Finally, Merck & Co., Inc.v. Olin Mathieson Chem. Corp., 253 F.2d 156, cited by Myriad, is entirely consistent with the principle set forth in Funk Brothers and American Fruit Growers that something derived from a product of nature must "possess a new or distinctive form, quality, or property" in order to become patentable subject matter. Am. Fruit Growers, 283 U.S. at 11. In Merck, the Fourth Circuit considered the validity of a patent claiming a Vitamin B12 composition useful for treating pernicious anemia. Id. at 157. Although naturally occurring Vitamin B12 produced in cows had known therapeutic properties and was commercially available, the court found the purified B12 composition, which was obtained from a microorganism, patentable. In upholding the validity of the patent, the court held:

> Every slight step in purification does not produce a new product. What is gained may be the old product, but with a greater degree of purity. Alpha alumina purified is still alpha alumina, In re Ridgway, 76 F.2d 602, [ ] and ultramarine from-which floatable impurities have been removed is still ultramarine, In re Merz, 97 F.2d 599 . . .

Id. at 163. Because the court concluded that the purified B12 was more than a "mere advance in the

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patents on pharmaceutical compounds such as vitamin B12" and adrenaline. See Bergy, 596 F.2d at 974-75 & n.13.

degree of purity of a known product," it determined that the claimed invention was entitled to patent protection. Id. at 164.

In sum, the clear line of Supreme Court precedent and accompanying lower court authorities, stretching from American Wood-Paper through to Chakrabarty, establishes that purification of a product of nature, without more, cannot transform it into patentable subject matter. Rather, the purified product must possess "markedly different characteristics" in order to satisfy the requirements of § 101.

3. The claimed isolated DNA is not "markedly different" from native DNA

The question thus presented by Plaintiffs' challenge to the composition claims is whether the isolated DNA claimed by Myriad possesses "markedly different characteristics" from a product of nature.[50] Chakrabarty, 447 U.S. at 310. In support of its position, Myriad cites several differences between the isolated DNA claimed in the patents and the native DNA found within human cells. None, however, establish the subject matter patentability of isolated *BRCA1/2* DNA.

The central premise of Myriad's argument that the claimed DNA is "markedly different" from DNA found in nature is the assertion that "[i]solated DNA molecules should be treated no differently than other chemical compounds for patent eligibility,"

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[50] The parties do not appear to dispute that isolated DNA claimed in the patents-in-suit are "useful" for purposes of § 101.

Myriad Br. at 26, and that the alleged "difference in the structural and functional properties of isolated DNA" render the claimed DNA patentable subject matter, Myriad Sr. at 31.

Myriad's focus on the chemical nature of DNA, however, fails to acknowledge the unique characteristics of DNA that differentiate it from other chemical compounds. As Myriad's expert Dr. Joseph Straus observed: "Genes are of double nature: On the one hand, they are chemical substances or molecules. On the other hand, they are physical carriers of information, i.e., where the actual biological function of this information is coding for proteins. Thus, inherently genes are multifunctional." Straus Decl. ¶ 20; see also *The Cell* at 98, 104 ("Today the idea that DNA carries genetic information in its long chain of nucleotides is 50 fundamental to biological thought that it is sometimes difficult to realize the enormous intellectual gap that it filled . . . . DNA is relatively inert chemically."); Kevin Davies & Michael White, *Breakthrough: The Race to Find the Breast Cancer Gene 166* (1996) (noting that Myriad Genetics' April 1994 press release described itself as a "genetic information business"). This informational quality is unique among the chemical compounds found in our bodies, and it would be erroneous to view DNA as "no different [ ]" than other chemicals previously the subject of patents.[51]

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[51] Myriad and many of the amici suggest that the invalidation of the patents-in-suit will result in the decimation of the biotechnology industry. See, e.g., Myriad Br. at 28-29 (suggesting that a finding that DNA is unpatentable subject matter will invalidate patents to important chemical

Myriad's argument that all chemical compounds, such as the adrenaline at issue in Parke-Davis, necessarily conveys some information ignores the biological realities of DNA in comparison to other chemical compounds in the body. The information encoded in DNA is not information about its *own* molecular structure incidental to its biological function, as is the case with adrenaline or other chemicals found in the body. Rather, the information encoded by DNA reflects its primary biological function: directing the synthesis of *other* molecules in the body namely, proteins, "biological molecules of enormous importance" which "catalyze biochemical reactions" and constitute the "major structural materials of the animal body." O'Farrell, 854 F.2d at 895-96. DNA, and in particular the ordering of its nucleotides, therefore serves as the physical embodiment of laws of nature – those that define the construction of the human body. Any "information" that may be embodied by adrenaline and similar molecules serves no comparable function, and none of the declarations submitted by Myriad support such a conclusion. Consequently, the use of simple analogies comparing DNA with chemical compounds previously the

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compounds such as the anticancer drug Taxol (paclitaxel) and leave "little to nothing" of the United States biotechnology industry). The conclusions reached in this opinion concerning the subject matter patentability of isolated DNA, however, are based on the unique properties of DNA that distinguish it from all other chemicals and biological molecules found in nature. As a result, Myriad's predictions for the future of the U.S. biotechnology industry are unfounded.

subject of patents cannot replace consideration of the distinctive characteristics of DNA.

In light of DNA's unique qualities as a physical embodiment of information, none of the structural and functional differences cited by Myriad between native *BRCA1/2* DNA and the isolated *BRCA1/2* DNA claimed in the patents-in-suit render the claimed DNA "markedly different." This conclusion is driven by the overriding importance of DNA's nucleotide sequence to both its natural biological function as well as the utility associated with DNA in its isolated form. The preservation of this defining characteristic of DNA in its native and isolated forms mandates the conclusion that the challenged composition claims are directed to unpatentable products of nature.

Myriad argues that the § 101 inquiry into the subject matter patentability of isolated DNA should focus exclusively on the differences alleged to exist between native and isolated DNA, rather than considering the similarities that exist between the two forms of DNA. See, e.g., Myriad Reply at 8-9 ("[T]he observation that isolated DNA and native DNA share this single property [i.e. the same protein coding sequences] is irrelevant to the critical issue of whether there are *differences* in their properties. It is the *differences* that are legally relevant to the novelty inquiry under Section 101, not the properties held in common." (emphasis in original)); Myriad Br. at 8. Setting aside the fact that considerations such as novelty are irrelevant for § 101 purposes, see Bergy, 126 596 F.2d at 960-61, Myriad offers no authorities supporting such an approach. To the contrary, the Supreme Court has held that "[i]n determining the eligibility of [a] claimed process for patent protection under § 101, [the] claims must be considered as a whole." Diehr, 450 U.S. at 188. Similarly, the Federal Circuit has expressly held that "[i]n the final analysis under § 101, the claimed invention, as a whole, must be evaluated for what it is." In re Grams, 888 F.2d 835, 839 (Fed. Cir. 1989) (quoting In re Abele, 684 F.2d 902, 907 (C.C.P.A. 1982)).

Were Myriad's approach the law, it is difficult to discern how any invention could fail the test. For example, the bacterial mixture in Funk Brothers was unquestionably different from any preexisting bacterial mixture; yet the Supreme Court recognized that a patent directed to the mixture, considered as a whole, did no more than patent "the handiwork of nature." 333 U. S. at 131. There will almost inevitably be some identifiable differences between a claimed invention and a product of nature; the appropriate § 101 inquiry is whether, considering the claimed invention as a whole, it is sufficiently distinct in its fundamental characteristics from natural phenomena to possess the required "distinctive name, character, [and] use." Chakrabarty, 447 U.S. at 309-10.

None of Myriad's arguments establish the distinctive nature of the claimed DNA. Myriad's argument that association of chromosomal proteins with native DNA establishes the existence of "structural differences" between native and isolated DNA relies on an incorrect comparison between isolated DNA and *chromatin*, which are indeed different insofar as chromatin includes chromosomal proteins normally associated with DNA. The proper comparison is between the claimed isolated DNA and the corresponding native DNA, and the presence or absence of chromosomal proteins merely constitutes a difference in purity that cannot serve to establish subject matter patentability. See Gen. Elec., 28 F.2d at 642-43; Marden I, 47 F.2d at 957-58; Marden II, 47 F.2d at 1059.

Myriad also attempts to rely on its assertion that native DNA contains intron sequences that are absent in the claimed *BRCA1/2* DNA. However, some of the claims, such as claim 1 of the '282 patent, are directed broadly to DNA "coding for a BRCA1 polypeptide." Native *BRCA1* DNA, by definition, encodes the *BRCA1* protein; thus claim 1 of the '282 patent would cover purified *BRCA1* DNA possessing the exact same structure found in the human cell, introns and all.[52] See also '492 patent, claim 1 (similarly claiming isolated DNA "coding for a BRCA2 polypeptide"). In addition, several of the composition claims are directed to isolated DNA containing as few as 15 nucleotides of the *BRCAI* coding sequence, see, e.g., '282 patent, claims 5 & 6, and at least some of these short DNA sequences will be found within a single exon of the native *BRCAI* gene sequence. See Adam Pavlicek, et al., Evolution of the Tumor Suppressor *BRCA1* Locus in Primates: Implications for Cancer Predisposition, 13 Human Molecular Genetics 2737, 2737 (2004) (noting *BRCAI* exons range from 37 to 3427 nucleotides in length). Therefore, for these small DNA fragments, the existence of introns in native *BRCA1* DNA is completely irrelevant to the question of structural differences when comparing these short DNA molecules with native *BRCA1* DNA.

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[52] To the extent a claim reads on unpatentable subject matter, the entire claim must be deemed invalid. See Titanium Metals Corp. of Am. v. Banner, 778 F.2d 775, 782 (Fed. Cir. 1985).

More generally, the fact that the *BRCA1/2* cDNA molecules covered by the composition claims-in-suit contain only the protein coding exons and not the introns found in native DNA does not render these cDNAs and their native counterparts "*markedly different*." The splice variants represented by these cDNAs are the result of the naturally occurring splicing of pre-mRNA into mature mRNA. Therefore, not only are the coding sequences contained in the claimed DNA identical to those found in native DNA, the particular arrangement of those coding sequences is the result of the natural phenomena of RNA splicing. Finally, at least in the case of *BRCA1*, the claimed cDNA sequences are actually found in the human genome in the form of a naturally occurring pseudogene. See Mason Supp. Decl. ¶ 18.[53]

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[53] Native DNA is sometimes methylated, but that methylation is preserved when the DNA is extracted and purified. Nussbaum Decl. ¶ 20. Since the claimed "isolated DNA" includes DNA extracted and purified from the body, methylation of DNA in the body does not distinguish native DNA from the claimed DNA. In addition, DNA in the body also exists in a non-methylated state, just as the synthesized DNA claimed in the patents would not be methylated. More importantly, while methylation affects the transcription of a gene in the body, it does not have any impact on the genetic information contained within the DNA. Indeed, DNA is demethylated and remethylated as it passes from the germline of one generation to the next. Nussbaum Decl. ¶ 28.

Myriad's argument that the functional differences between native and isolated DNA demonstrates that they are "markedly different" relies on the fact that isolated DNA may be used in applications for which native DNA is unsuitable, namely, in "molecular diagnostic tests (e.g., as probes, primers, templates for sequencing reactions), in biotechnological processes (e.g. production of pure *BRCA1* and *BRCA2* protein), and even in medical treatments (e.g. gene therapy)." Myriad Reply at 9; see also Myriad Br. at 30-32.

Isolated DNA's utility as a primer or a molecular probe (for example, for Southern blots) arises from its ability to "target and interact with other DNA molecules," that is, the ability of a given DNA molecule to bind exclusively to a specific DNA target sequence. Myriad Br. at 33; see Kay Decl. ¶ 138. Thus, for example, a 24 nucleotide segment of isolated *BRCAI* DNA can be used as a primer because it will bind only to its corresponding location in the *BRCAI* gene. However, the basis for this utility is the fact that the isolated DNA possesses the identical nucleotide sequence as the target DNA sequence,[54] thus allowing target specific hybridization between the DNA primer and the portion of the target DNA molecule possessing the corresponding sequence. Kay Decl. ¶¶ 135-36, 138. In contrast, another 24 nucleotide segment of DNA possessing the same nucleotide composition but a different nucleotide sequence would not have the same utility because it would be unable to hybridize to the proper location in the *BRCA1* gene.[55] Indeed, Myriad implicitly acknowledges this fact when it states that the usefulness of isolated DNA molecules "is based on their ability to target and interact with other DNA molecules, which is a function of *their own individual structure and chemistry.*" Myriad Br. at 33 (emphasis added). Therefore, the cited utility of the isolated DNA as a primer or probe is primarily a function of the nucleotide sequence identity between native and isolated *BRCA1/2* DNA.

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[54] To be precise, the isolated single-stranded DNA molecule utilized as a primer or probe has the identical sequence as the complementary DNA strand to the DNA strand containing the target DNA sequence. The description in the text is meant to serve as a shorthand description of this relationship.

Similarly, the utility of isolated DNA as a sequencing target relies on the preservation of native DNA's nucleotide sequence. Indeed, one need look no further than Myriad's BRACAnalysis testing, which relies on the sequencing of isolated DNA (i.e. the PCR amplified exons of *BRCA1/2),* to determine the sequence of the corresponding DNA coding sequences found in the cell. The entire premise behind Myriad's genetic testing is that the claimed isolated DNA retains, in all relevant respects, the identical nucleotide sequence found in native DNA. The use of isolated *BRCA1/2* DNA in the production of BRCA1/2 proteins or in gene therapy also relies on the identity between the native DNA sequences and the sequences contained in the isolated DNA molecule. Were the isolated *BRCA1/2* sequences different in any significant way, the entire point of their use the production of *BRCA1/2* proteins - would be undermined.

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[55] The same reasoning applies with respect to the use of isolated DNA as a probe. Kay Decl. ¶¶ 135-36.

While the absence of proteins and other nucleotide sequences is currently required for DNA to be useful for the cited purposes, the purification of native DNA does not alter its essential characteristic – its nucleotide sequence that is defined by nature and central to both its biological function within the cell and its utility as a research tool in the lab. The requirement that the DNA used be "isolated" is ultimately a technological limitation to the use of DNA in this fashion, and a time may come when the use of DNA for molecular and diagnostic purposes may not require such purification. The nucleotide sequence, however, is the defining characteristic of the isolated DNA that will always be required to provide the sequence-specific targeting and protein coding ability that allows isolated DNA to be used for the various applications cited by Myriad. For these reasons, the use of isolated DNA for the various purposes cited by Myriad does not establish the existence of differences "in kind" between native and isolated DNA that would establish the subject matter patentability of what is otherwise a product of nature. See Am. Fruit Growers, 283 U.S. at 11.

Finally, the isolated *BRCA1/2* DNA claimed in Myriad's patents bears comparison to the bacterial mixture in Funk Brothers. In explaining why the claimed mixture of bacteria did not constitute an invention, the Court observed that the first part of the claimed invention was the "[d]iscovery of the fact that certain strains of each species of these bacteria can be mixed without harmful effect to the properties of either" which was "a discovery of their qualities of non-inhibition. It is no more than the discovery of some of the handiwork of nature and hence is not patentable." 33 U.S. at 131. The Court went on to observe that the second part of the claimed invention was [t]he aggregation of select strains of the several species into one product[,] an application of that newly discovered natural principle. But however ingenious the discovery of that natural principle may have been, the application of it is hardly more than an advance in the packaging of the inoculants." Id.

According to Myriad, the invention claimed in its patents required the identification of the specific segments of chromosomes 17 and 13 that correlated with breast and ovarian cancer *(BRCA1* and *BRCA2)* followed by the isolation of these sequences away from other genomic DNA and cellular components. Myriad Reply at 6 ("By identifying these particular *BRCA* DNAs and isolating them away from other genomic DNA and other cellular components, the inventors created the claimed isolated *BRCA* DNA molecules."). Like the discovery of the mutual non-inhibition of the bacteria in Funk Brothers, discovery of this important correlation was a discovery of the handiwork of nature - the natural effect of certain mutations in a particular segment of the human genome. And like the aggregation of bacteria in Funk Brothers, the isolation of the *BRCA1* and *BRCA2* DNA, while requiring technical skill and considerable labor, was simply the application of techniques well-known to those skilled in the art. See Parthasarathy Decl. ¶ 19. The identification of the *BRCA1* and *BRCA2* gene sequences is unquestionably a valuable scientific achievement for which Myriad deserves recognition, but that is not the same as concluding that it is something for which they are entitled to a patent. See Funk Bros., 33 U.S. at 132 ("[O]nce nature's secret of the non-inhibitive quality of certain strains of the [nitrogen-fixing bacteria] was discovered, the state of the art made the production of a mixed inoculant a simple step. Even though it may have been the product of skill, it certainly was not the product of invention.").

Because the claimed isolated DNA is not markedly different from native DNA as it exists in nature, it constitutes unpatentable subject matter under 35 U.S.C. § 101.

D. The Method Claims are Invalid Under 35 U.S.C. § 101

"Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." Benson, 409 U.S. at 67. However, "'an application of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection.'" Bilski, 545 F.3d at 953 (quoting Diehr, 450 U.S. at 187). In Bilski, the Federal Circuit set forth "the definitive test to determine whether a process claim is tailored narrowly enough to encompass only a particular application of a fundamental principle rather than pre-empt the principle itself." Id. at 954. Under this "machine or transformation" test, "[a] claimed process is surely patent-eligible under § 101 if: (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing." Id. In addition, "the use of a specific machine or transformation of an article must impose meaningful limits on the claim's scope to impart patent-eligibility," and "the involvement of the machine or transformation in the claimed process must not merely be insignificant extra-solution activity." Id. at 961-62. In other words, the "transformation must be central to the purpose of the claimed process." Id. at 962. In particular, the Bilski court held that "adding a data-gathering step to an algorithm is insufficient to convert that algorithm into a patent-eligible process." Id. at 963 (citing Grams, 888 F.2d at 840; Meyer, 688 F.2d at 794). "A requirement simply that data inputs be gathered - without specifying how is a meaningless limit on a claim to an algorithm because every algorithm inherently require the gathering of data inputs." Id. (citing Grams, 888 F.2d at 839-40). "Further, the inherent step of gathering data can also fairly be characterized as insignificant extra-solution activity." Id. (citing Flook, 437 U.S. at 590).

1. The claims for "analyzing" and "comparing" DNA sequences are invalid under § 101

Claim 1 of the '999 patent is directed to the process of "analyzing" a *BRCA1* sequence and noting whether or not the specified naturally-occurring mutations exist. The claimed process is not limited to any particular method of analysis and does not specify any further action beyond the act of "analyzing." Similarly. claim 1 of the '001, '441, and '857 patents as well as claim 2 of the '857 patents are directed to "comparing" two gene sequences to see if any differences exist and do not specify any limitations on the method of comparison.

Myriad argues that these method claims should not be viewed as mental processes because they incorporate a transformation step and therefore satisfy the "transformation" prong of the Bilski "machine or transformation" test. In support of its position, Myriad relies primarily on the Federal Circuit's holding in Prometheus, 581 F.3d 1336. There, the Federal Circuit considered a patent containing claims directed to methods for calibrating the proper dosage of thiopurine drugs by measuring metabolites in subjects having gastrointestinal disorders. Id. at 1343-50. The patentees had discovered a correlation between metabolite levels in a patient's blood and the therapeutic efficacy of a dose of the drug. Based on this correlation, the patentees claimed methods to optimize therapeutic efficiency while minimizing side effects by determining metabolite levels and identifying a need to adjust drug dosage upward or downward based on the levels. Id. at 1339-40. A representative claim asserted by the patentee in Prometheus claimed:

> A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
>
> (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,
>
> wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug

> subsequently administered to said subject
>
> and
>
> wherein the level of 6-thioguanine greater than about 400 pmol per 8xl08 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Id. at 1340.

In concluding that the claimed methods satisfied the requirements of § 101, the Federal Circuit held that the relevant transformation for purposes of the "machine or transformation" test was the transformation of the human body as well as the chemical and physical changes of the drug's metabolites. Id. at 1346 (stating that "claims to methods of treatment," were "always transformative when a defined group of drugs is administered to the body to ameliorate the effects of an undesired condition'". Because the transformative steps were central to the claimed treatment methods, they satisfied the "machine or transformation" test. Id. at 1346-47. The court went on to hold that the "determining" step alone was transformative and central to the claimed methods since "determining the levels of [the metabolites] 6-TG or 6-MMP in a subject necessarily involves a transformation, for those levels cannot be determined by mere inspection." Id. at 1347.

Myriad argues that just as the act of "determining" metabolite levels in Prometheus was found to involve the transformation of human blood, so too should "analyzing" or "comparing" *BRCA1/2* gene sequences be construed to incorporate physically transformative steps (i.e. the isolation and sequencing of DNA[56]) that would satisfy the Bilski "machine or transformation" test. Myriad further asserts that these transformations are "central to the purpose of the claims," id. at 1347, because "Myriad's method claims each require the transformation of a tissue or blood sample in order to isolate the patient's DNA." Myriad Br. at 35.

The claims in Prometheus, however, are distinguishable from the method claims in dispute here. In Prometheus, "determining metabolite levels in the clinical samples taken from patients" was found to be transformative because the act of "determining metabolite levels" was itself construed to include the extraction and measurement of metabolite concentrations, such as high pressure liquid chromatography. See Prometheus, 581 F.3d at 1347. Indeed, neither party in Prometheus disputed that "determining" metabolite levels in samples taken from patients was, in and of itself, transformative."[57]

In contrast, the language of the method claims-in-suit and the plain and ordinary meanings of the terms "analyzing" or "comparing" establish that the method claims-in-suit are directed only to the abstract mental processes of "comparing" or "analyzing" gene sequences. Although Myriad asserts that the challenged method claims are directed to comparing DNA molecules rather than DNA sequences, the language of the claims belies such an interpretation. While the purpose of the claimed method is, for example, to "detect a germline alteration in a BRCA1 gene," see '999 patent, col. 161: 17-18, the *method* actually claimed is "analyzing a *sequence* of a BRCA1 gene." '999 patent, col. 161: 20-21 (emphasis added); see also '001 patent, col. 144:2-17 ("A method . . . which comprises gene comparing a first sequence selected from the group consisting of a BRCA1 gene from said tumor sample with a second sequence selected from the group consisting of BRCA1 gene from a nontumor sample . . . wherein a difference in the sequence of the BRCA1 gene . . . indicates a somatic alteration in the BRCA1 gene."); '857 patent, col. 169:40-45 ("A method . . . which comprises comparing the nucleotide sequence of the suspected mutant BRCA2 allele with the wild-type BRCA2 nucleotide sequence . . . ").

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[56] The challenged method claims are also directed to analyzing and comparing RNA and cDNA sequences, but for purposes of this opinion, the discussion will be framed in terms of analyzing and comparing DNA sequences.

[57] The issue with respect to the "determining" step was not whether it was transformative, but whether that transformation was central to the claimed invention. Id.

Similarly, the inclusion of the phrases "from a human subject" or "from a nontumor sample" in the claims serve only to specify the identity of the DNA or RNA sequence to be "analyzed" or "compared," i.e., from a human sample as opposed to an animal sample or cell culture, and do not, as Myriad argues, establish that the claims should be read to include the physical transformations associated with obtaining DNA from those sources.[58] In addition, the passages from the '999 specification cited by Myriad describing the process by which DNA sequences are obtained cannot serve to redefine the scope of the challenged claims without violating the prohibition against importing claim limitations from the specification. See Phillips, 415 F.3d at 1320.

By the same token, the transformative steps associated with isolating and sequencing DNA described in the unchallenged dependent claims cannot be used to establish that the challenged claims include trans formative events. To do so would violate the doctrine of claim differentiation, which presumes that "different words or phrases used in separate claims . . . indicate that the claims have different meanings and scope." Karlin Tech., Inc. v. Surgical Dynamics, Inc., 177 F.3d 968, 972 (Fed. Cir. 1999). Because claim differentiation "prevents the narrowing of broad claims by reading into them the limitations of narrower claims," Clearstream Wastewater Sys., Inc. v. Hydro-Action, Inc., 206 F.3d

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[58] Whether acts are "transformative" in the context of the "machine or transformation" test for process claims is distinct from the question of whether those acts would render the resulting product patentable subject matter. See, e.g., Am. Wood-Paper, 90 U.S. (23 Wall.) at 593-94 (noting that a party may be entitled to a patent on a process for purifying a natural product but not the final product itself if the final product is not different "in kind" from the natural product); Merz, 97 F.2d at 601 (same). Therefore the description of DNA purification and sequencing as "transformative acts" in the context of the challenged process claims is not inconsistent with the conclusion that the isolated DNAs claimed in the challenged patents constitute unpatentable subject matter.

1440, 1446 (Fed. Cir. 2000), the dependent claims serve only to illustrate the breadth of the challenged claims and reinforce the conclusion that what is claimed are mental processes independent of any physical transformations. See Phillips, 415 F.3d at 1314-15 ("[T]he presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim.").[59]

Myriad also argues that because isolating and sequencing DNA are required for "analyzing" or "comparing" DNA sequences, Prometheus allows those transformative acts to be incorporated into the process claims for purposes of the § 101 analysis. See Myriad Reply at 12. Myriad thus seeks to rely on transformations not actually claimed by the method claims-in-suit to satisfy the Bilski "machine or transformation" test. Neither Prometheus nor any other authority supports such an expansive approach to the application of this test. Prometheus held only that the term "determining," as used in the claims at issue, referred to acts that included manipulations that satisfied the "machine or transformation" test. Id. Nowhere did Prometheus suggest that preparatory physical transformations required for the performance of, but not included in, claims directed to mental processes should be incorporated into the claim for purposes of the § 101 analysis. Not only would such an approach be inconsistent with the prohibition on the importation of claim limitations from the specification, it would effectively vitiate the limitations to claiming mental processes provided by the "machine or transformation" test since "to use virtually any natural phenomenon for virtually any useful purpose could well involve the use of empirical information obtained through an unpatented means that might have involved transforming matter." Metabolite Labs., 548 U.S. at 136 (Breyer, J., dissenting). Therefore the preparatory transformations relating to obtaining DNA sequences cannot be relied on to satisfy the requirements of § 101.

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[59] The patent examiner's reasons for allowance, cited by Myriad, are precisely the legal conclusions concerning the patentability of the claimed methods being challenged by Plaintiffs. Moreover, the examiner's reasons of allowance cannot serve to define the scope of claim terms. See ACCO Brands, Inc. v. Micro Sec. Devices, Inc., 346 F.3d 1075, 1079-(Fed. Cir. 2003).

Even if the challenged method claims were read to include the transformations associated with isolating and sequencing human DNA, these transformations would constitute no more than "data-gathering step[s]" that are not "central to the purpose of the claimed process." Bilski, 545 F.3d at 962-63. In Grams, the Federal Circuit considered a patent directed to a method of diagnosing an abnormal condition in an individual. The claimed method consisted of two steps: (1) "performance of Clinical laboratory tests on an individual to obtain data for the parameters," and (2) "analyz[ing] that data to ascertain the existence and identity of an abnormality . . . ." 888 F.2d at 837. Concluding that the essence of what was claimed was the mathematical algorithm for analyzing the clinical data, and that the sole physical process laboratory testing - was merely data-gathering to obtain clinical data, the court held the patent invalid under § 101 for claiming a mathematic algorithm. Id. at 840.

The method claims-in-suit present a closely analogous situation. The essence of what is claimed is the identification of a predisposition to breast cancer based on "analyzing" or "comparing" *BRCA1/2* gene sequences. See, e.g., '857 patent, claim 2 ("A method for diagnosing a predisposition for breast cancer in a human subject which comprises comparing the [BRCA2 gene sequence] from said subject with the [ ] sequence of the wild-type BRCA2 gene . . . ."). As in Grams, isolation and sequencing of DNA from a human sample, even if incorporated into the method claims-in-suit, would represent nothing more than data-gathering steps to obtain the DNA sequence information on which to perform the claimed comparison or analysis. Moreover, in the absence of a specified method for isolating and sequencing DNA, "[a] requirement simply that data inputs be gathered without specifying how is a meaningless limit on a claim to an algorithm because every algorithm inherently requires the gathering of data inputs." Bilski, 545 F.3d at 963 (citing Grams, 888 F.2d at 839-40). Consequently, even if the method claims-in-suit were construed to include the physical transformations associated with isolating and sequencing DNA, they would still fail the "machine or transformation" test under § 101 for subject matter patentability.

2. The Claim for "Comparing" the growth rate of Cells is invalid under § 101

Claim 20 of the '282 patent is directed to "comparing" the growth rates of cells in the presence or absence of a potential cancer therapeutic. Specifically, the claim recites a method for identifying potential cancer therapeutics by utilizing cells into which an altered *BRCA1* gene known to cause cancer has been inserted. Thus modified to mimic cancerous cells in the body, these cells are then grown in either the presence or absence of a potential cancer therapeutic, and the growth rates of the cells are compared to determine the effect of the potential therapeutic.

Unlike the method claims directed to "analyzing" or "comparing" DNA sequences, claim 20 arguably recites certain transformative steps, such as the administration of the test compound.[60] However, the essence of the claim, when considered in its entirety, is the act of comparing cell growth rates and concluding that "a slower growth of said host cell in the presence of said compound is indicative of a cancer therapeutic." '282 patent, col. 156: 25-27.

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[60] It is questionable whether the two transformations cited by Myriad are relevant transformations for purposes of the § 101 inquiry. Under Prometheus, the administration of a test compound is transformative only if it effects a change in cell growth. See Prometheus, 581 F.3d at 1346 (finding "administering" of a drug transformative since it resulted in changes to both the patient and the drug metabolites). If the test compound had no effect on the cells, it is unclear whether there would be any basis to view its administration as working a "transformation" since there would be no transformation with respect to the cells (i.e. there was no change in their growth rate) and there would also presumably be no transformation with respect to the test drug (i.e, it was not metabolized).

The other alleged "transformation" cited by Myriad is the insertion of DNA into cells to create the "transformed eukaryotic cell" for treatment with the test compound. Kay Decl. ¶ 57. Even more that its expansive interpretation of the method claims for analyzing DNA sequences for § 101 purposes, Myriad's attempt to rely on transformations associated with the creation of a starting product for its claimed process is unsupported by the law and demonstrates the limitlessness of Myriad' s interpretation of Prometheus and the "machine or transformation" test.

This claimed "process" is, in fact, the scientific method itself, and claim 20 seeks to patent a basic scientific principle: that a slower rate of cell growth in the presence of a compound indicates that the compound may be a cancer therapeutic. The recited transformative steps, as in Grams, represent nothing more than preparatory, data-gathering steps to obtain growth rate information and do not render the claimed mental process patentable under § 101. See Grams, 888 F.2d at 840 ("The presence of a physical step in the claim to derive data for the algorithm will not render the claim statutory").[61]

E. The Constitutional Claims Against the USPTO Are Dismissed

As determined above, the patents issued by the USPTO are directed to a law of nature and were therefore improperly granted. The doctrine of constitutional avoidance, which states that courts should not reach unnecessary constitutional questions, thereby becomes applicable. See, e.g., Allstate Ins. Co. v. Serio, 261 F.3d 143, 149-50 (2d Cir. 2001) ("It is axiomatic that the federal courts should, where possible, avoid reaching constitutional questions.") (citing Sector Motor Serv., Inc. v. McLaughlin, 323 U.S. 101 (1944) ("If there is one doctrine more deeply rooted than any other in the process of constitutional adjudication, it is that we ought not to pass on questions of constitutionality . . . unless such adjudication is unavoidable")); see also Ashwander v. TVA, 297 U.S. 288,347 (1936) (Brandeis, J., concurring) ("[I]f a case can be decided on either of two grounds, one involving a constitutional question, the other a question of statutory construction or general law, the Court will decide only the latter."). This doctrine bears on the consideration of Plaintiffs' claims that the USPTO's policy permitting the grant of the Myriad patents violates Article I, Section 8, Clause 8 and the First Amendment of the Constitution.

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[61] Because Plaintiffs' motion for summary judgment with respect to its claims against Myriad is granted on the basis of 35 U.S.C. § 101, its Constitutional claims need not be addressed.

The Plaintiffs have not addressed these authorities and have contended that "the doctrine of constitutional avoidance is inapplicable" because the invalidation of Myriad's claims pursuant to 35 U.S.C. § 101 will not necessarily invalidate the USPTO's policy [in granting the patents]." Pl. Reply at 43. However, a decision by the Federal Circuit or the Supreme Court affirming the holding set forth above would apply to both the issued patents as well as patent applications and would be binding on all patent holders and applicants, as well as the USPTO. See Koninklijke Philips Electronics N.V. v. Cardiac Science, 590 F.3d 1326, 1337 (Fed. Cir. 2010) ("We remind the district court and the [USPTOl Board that they must follow judicial precedent. . . ."). Thus, to the extent the USPTO examination policies are inconsistent with a final, binding ruling, the USPTO would conform its examination policies to avoid issuing patents directed to isolated DNA or the comparison or analysis of DNA sequences. See USPTO Reply Memo, at 4.

With the holding that the patents are invalid, the Plaintiffs have received the relief sought in the Complaint and the doctrine of constitutional avoidance precludes this Court from reaching the constitutional claims against the USPTO. See Allstate Ins. Co. v. Serio, 261 F.3d 143, 149-50 (2d Cir. 2001); USPTO Br. at 4. Plaintiffs' claims for constitutional violations against the USPTO are therefore dismissed without prejudice.

VIII. CONCLUSION

For the reasons set forth above, Plaintiffs' motion for summary judgment is granted in part, Myriad's motion for summary judgment is denied, the USPTO's motion for judgment on the pleadings is granted, and the claims-in-suit are declared invalid pursuant to 35 U.S.C. § 101.

Submit judgment on notice.

It is so ordered.

New York, N.Y.

April 2, 2010

Robert W. Sweet

U.S.D.J.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

ASSOCIATION FOR MOLECULAR PATHOLOGY, ET. AL.,
Plaintiffs,

09 Civ. 4515
OPINION

--against--

UNITED STATES PATENT AND TRADEMARK OFFICE, ET AL.,
Defendants.

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Sweet, D.J.

In this action the Plaintiffs challenge certain patent claims granted to defendants Myriad Genetics and the Director[1] of the University of Utah Research Foundation ("UURF") (collectively, "Myriad") by defendant United States Patent and Trademark Office ("USPTO") (collectively, the "Defendants"). The identified patent claims (the "patents-in-suit" or the "claims-in-suit") cover two human genes known as *BRCA1* and *BRCA2* (collectively, *"BRCA1/2"* or the *"BRCA* genes"). Compl. ¶¶ 37, 55-80. The claims-in-suit also cover certain mutations in those genes, the mental act of comparing different forms of the *BRCA* genes, and the correlations between certain genetic mutations and an increased risk of breast and/or ovarian cancer. Id.

The Plaintiffs allege that these patents are unlawful under each of (1) the Patent Act, 35 U.S.C. § 101 (1952), (2) Article I, Section 8, Clause 8 of the United States Constitution, and (3) the First and Fourteenth Amendments because they cover products of nature, laws of nature and/or natural phenomena, and abstract ideas or basic human knowledge or thought. Compl. ¶ 102.

The Defendants now move, pursuant to Rules 12 (b) (1), (b) (2), and (b) (6), Fed. R. Civ. P., to dismiss Plaintiffs' complaint (the "Complaint") for lack of subject matter jurisdiction, lack of personal jurisdiction, and failure to state a claim.

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[1] Defendants Lorris Betz, Roger Boyer, Jack Brittan, Arnold B. Combe, Raymond Gesteland, James U. Jenson, John Kendall Morris, Thomas Parks, David W. Pershing, and Michael K. Young. For purposes of this opinion, they will be referred to as the "Directors" or the "UURF Directors."

This action is unique in the identity of the parties, the scope and significance of the issues presented, and the consequences of the remedy sought. The Plaintiffs in this action comprise a broad range of parties, including researchers, genetic counselors, medical and/or advocacy organizations, and women facing the threat of breast cancer or who are in the midst of their struggle with the illness. The challenges to the patents-in-suit raise questions of difficult legal dimensions concerning constitutional protections over the information that serves as our genetic identities and the need to adopt policies that promote scientific innovation in biomedical research. The widespread use of gene sequence information as the foundation for biomedical research means that resolution of these issues will have far-reaching implications, not only for gene-based health care and the health of millions of women facing the specter of breast cancer, but also for the future course of biomedical research.

Based on the conclusions set forth below, the motions to dismiss are denied.

I. PRIOR PROCEEDINGS

The Complaint in this action was filed on May 12, 2009.

The Plaintiffs moved for summary judgment pursuant to Rule 56, Fed. R. Civ. P., on August 26, 2009.

Defendants' motion to dismiss and Plaintiffs' motion for jurisdictional discovery[2] were heard and marked fully submitted on September 30, 2009, and Plaintiffs' motion for summary judgment was stayed pending resolution of Defendants' motion to dismiss.

II. THE COMPLAINT AND THE AFFIDAVITS

The following allegations, taken from the Complaint and the affidavits submitted by the parties in connection with Defendants' motion to dismiss, are accepted as true for the purpose of resolving the motions to dismiss.

A. The Plaintiffs

Plaintiff the Association for Molecular Pathology ("AMP") is a not-for-profit scientific society dedicated to the advancement, practice, and science of clinical molecular laboratory medicine and translational research based on the applications of genomics and proteomics. AMP members participate in basic and translational research aimed at broadening the understanding of gene/protein structure and function, disease processes, and molecular diagnostics, and provide clinical medical services for patients, including diagnosis of breast cancer. Compl. ¶ 7.

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[2] Defendants' motion to dismiss incorporates, by reference, challenges to the exercise of personal jurisdiction over the Directors raised in Defendants' opposition to Plaintiffs' motion for jurisdictional discovery. Consequently, the arguments concerning personal jurisdiction set forth by the parties in connection with Plaintiffs' motion for jurisdictional discovery will be considered here.

Plaintiff the American College of Medical Genetics ("ACMG") is a non-profit organization of clinical and laboratory geneticists seeking to improve health through the practice of medical genetics. AMCG strives to 1) promote excellence in medical genetics practice and the integration of translational research into practice; 2) promote and provide medical genetics education; 3) increase access to medical genetics services and integrate genetics into patient care; and 4) advocate for and represent providers of medical genetics services and their patients. Compl. ¶ 8.

Plaintiff the American Society for Clinical Pathology ("ASCP") is the largest and oldest organization representing pathologists and laboratory professionals. ASCP members design and interpret the tests that detect disease, predict outcome, and determine the appropriate therapy for the patient. Compl. ¶ 9.

Plaintiff the College of American Pathologists ("CAP") is a national medical society representing board-certified pathologists and pathologists in training who practice anatomic pathology and laboratory medicine worldwide. The CAP is an advocate of high-quality and cost-effective medical care. Compl. ¶ 10.

The affidavits submitted by the Plaintiffs state that members of AMP, ACMG, ASCP, and CAP are ready, willing, and able to engage in research and clinical practice involving the *BRCA1/2* genes if the patents-in-suit were to be invalidated. For example, Madhuri Hegde, Ph.D. ("Dr. Hegde"), is a member of AMP and ACMG and serves as an Associate Professor in the Department of Human Genetics at

Emory University School of Medicine, Adjunct Assistant Professor at the University of Texas M.D. Anderson Cancer Center, and Senior Laboratory Director at the Emory Genetics Laboratory. He currently conducts research on human genes in addition to supervising one of the largest and most technologically advanced clinical laboratories in the country. The laboratory sequences and analyzes approximately sixty genes every day for sequence variants and their clinical significance. Dr. Hegde has personally sequenced the *BRCA1/2* genes while at the Auckland Hospital in New Zealand, and his lab would begin sequencing and analyzing *BRCA1/2* genes for clinically significant variants within weeks if the patents-in-suit were invalidated. Hegde Decl. ¶¶ 3-12.[3]

Roger Hubbard, Ph.D. ("Dr. Hubbard"), a member of ASCP, is the President and Chief Executive Officer, Molecular Pathology Laboratory Network, Inc. ("MPLN"), and an Adjunct Associate Professor at the University of Tennessee Medical Center/Knoxville, Department of Pathology. MPLN offers molecular diagnostics and cytogenetic testing services that target hematological malignancies, oncology, and medical diseases. MPLN currently sequences genes and has the personnel, experience and equipment to analyze the *BRCA* genes. They currently receive inquiries every few weeks from a hospital or laboratory asking them to analyze the BRCA genes, but they do not do so as solely because of the patents-in-suit. If the patents-in-suit were to be invalidated, Dr. Hubbard and MPLN would immediately consider doing testing in their laboratory. Hubbard ¶¶ 1-4, 6, 8-9.

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[3] For purposes of this opinion, references to the parties' declarations will be in the format [Declarant Name] ¶ [paragraph number].

Jeffrey Kant, M.D., Ph.D. ("Dr. Kant"), a member of AMP and CAP, is the Director of the Division of Molecular Diagnostics in the Department of Pathology at the University of Pittsburgh Medical Center and a Professor Pathology and Human Genetics at the University of Pittsburgh. As part of his responsibilities, he supervises a clinical laboratory that analyzes human genes and is experienced in sequencing and analyzing genes for inherited diseases. His laboratory currently tests nine genes, including five related to hereditary predisposition for cancer. His laboratory was asked in the late 1990s to engage in the sequencing and analysis of *BRCA 1/2*, but declined to do so because of the patents-in-suit. If the patents-in-suit were to be invalidated, Dr. Kant would immediately consider doing full gene testing for the *BRCA* genes. Kant ¶¶ 1-2, 4-6.

Plaintiff Haig Kazazian, Jr., M.D. ("Dr. Kazazian"), is the Seymour Gray Professor of Molecular Medicine in Genetics in the Department of Genetics at the University of Pennsylvania School of Medicine. He is the previous chair of the Department. Kazazian ¶ 1, 2. Plaintiff Arupa Ganguly, Ph.D. ("Dr. Ganguly"), is an Associate Professor in the Department of Genetics at the Hospital of the University of Pennsylvania. Ganguly ¶ 1. Drs. Kazazian and Ganguly have served as co-Directors of the University of Pennsylvania Genetic Diagnostic Laboratory ("GDL") since 1995. Kazazian ¶ 3; Ganguly ¶ 2. The GDL provides state-of-the-art DNA-based diagnostic testing for a variety of genetic conditions and diseases, as well as prenatal and predictive testing and genetic counseling services. Kazazian ¶ 3. Starting in 1996, the GDL was providing *BRCA1* genetic testing services to approximately 500 women per year. Id. ¶ 4. By late 1996, the GDL had designed and provided a similar test for the *BRCA2* gene. Id. Following Dr. Kazazian's and the University of Pennsylvania's receipt of a series of cease-and-desist letters from Myriad in 1998 and 1999, described infra, the GDL ceased its *BRCA1/2* genetic testing services. Id. ¶ 5-7; Ganguly ¶ 4-10. If the patents-in-suit were to be invalidated, the GDL possesses the technological capability necessary to begin performing *BRCA1/2* testing again within a matter of weeks, and Drs. Ganguly and Kazazian have the desire to consider doing so. Kazazian ¶ 11; Ganguly ¶ 14.

Plaintiff Wendy Chung, M.D., Ph.D. ("Dr. Chung"), is the Herbert Irving Professor of Pediatrics and Medicine in the Division of Molecular Genetics at Columbia University and is the Director of Clinical Genetics and Director of Clinical Oncogenetics. She is also a member of ACMG. Dr. Chung is a human geneticist whose current research includes research on the *BRCA* genes, for which she has received grants of over $1 million. Dr. Chung is a co-investigator of the Breast Cancer Family Registry, funded by the National Cancer Institute of the National Institute of Health. The goal of the Registry is to collect and study families with multiple cases of breast and/or ovarian cancer and to study genetic and environmental factors influencing cancer susceptibility and clinical outcomes. As part of her research, Dr. Chung's lab sequences human genes, including the *BRCA1/2* genes of research subjects to determine whether there exist alterations in the gene sequences and investigate their clinical significance. Because of the patents-in-suit, Dr. Chung does not tell the research subjects in her studies the results of the analysis of their *BRCA* genes. Dr. Chung's clinical diagnostic laboratory at Columbia University sends samples to Myriad for any analysis of *BRCA1/2* in order to tell the subjects the results and use the results clinically. It does not do BRCA testing on its own because of the patents-in-suit. If the patents-in-suit were to be invalidated, Dr. Chung would begin clinical testing of *BRCA1/2* immediately. Her clinical laboratory has the personnel, expertise to do various forms of *BRCA1/2* sequencing and would be able to offer genetic testing that is more comprehensive than the testing currently offered by Myriad. Chung Decl. ¶ 1, 4, 8-9, 11-14, 16-18.

Plaintiff Harry Ostrer, M.D. ("Dr. Ostrer"), is a Professor of Pediatrics, Pathology and Medicine, Director of the Human Genetics Program in the Department of Pediatrics at the New York University ("NYU") Langone Medical Center, and a member of ACMG. As Director of the Human Genetics Program, Dr. Ostrer helped establish the Molecular Genetics Laboratory ("MGL") at the NYU Langone Medical Center, one of the largest academic genetic testing laboratories in the United States. Dr. Ostrer's work through the MGL has focused on understanding the genetic basis of development and disease, including genetic susceptibility to breast cancer. Dr. Ostrer is actively engaged in identifying genes that convey the risk of breast cancer and may mitigate the effects of mutations in *BRCA1/2*. His laboratory has the ability to evaluate *BRCA1/2* gene sequences, including in custom-designed tests that may be more cost-effective than Myriad's current offerings. However, because of Myriad's assertions of the patents-in-suit, Dr. Ostrer sends all of his patient samples to Myriad for *BRCA1/2* analysis. If the patents-in-suit were to be invalidated, Dr. Ostrer would immediately begin clinical sequencing of the BRCA1/2 genes. His laboratory possesses all of the personnel, expertise, and facilities necessary to do various types of sequencing of the *BRCA1/2* genes, including full sequencing, detection of deletions and rearrangements, and searches for large rearrangements that Myriad currently does not offer as a service. If the patents-in-suit were to be invalidated, Dr. Ostrer would also tell patients involved in his current research program the results of their *BRCA1/2*-related genetic screening. Ostrer Decl. ¶¶ 1-5; 8-10.

Plaintiff David Ledbetter, Ph. D. ("Dr. Ledbetter"), is the Robert W. Woodruff Professor of Human Genetics and Director of the Division of Medical Genetics at the Emory University School of Medicine. He is also a diplomat of the American Board of Medical Genetics (Clinical Cytogenetics) and a Founding Fellow of the ACMG. He has previously served as the Director of the Kleberg Cytogenetics Laboratory at Baylor College of Medicine and in the Senior Executive Service of the federal government as Branch Chief of the Diagnostic Development Branch at the National

Center for Human Genome Research (now the National Human Genome Research Institute). He was also the founding Chair of the Department of Human Genetics at the University of Chicago where he held the Marjorie I. and Bernard A. Mitchell Professor of Human Genetics. As Director of the Division of Medical Genetics, Dr. Ledbetter is responsible for very large genetic testing laboratories at the Emory University School of Medicine which provide clinical testing services for patients and families with genetic diseases, including biochemical, cytogenetics, and molecular genetics testing. The genetic testing laboratory utilizes state-of-the-art technology and has the personnel, experience, expertise, and facilities necessary to conduct comprehensive mutation analysis (including full gene sequencing and high-resolution deletion/duplication analysis) of any human gene, including the *BRCA* genes. If the patents-in-suit were to be invalidated, Dr. Ledbetter would begin offering comprehensive *BRCA1/2* testing and would likely have an operational program within one month's time. Ledbetter Decl. ¶¶1, 3-4, 8-10, 18.

Plaintiff Stephen T. Warren, Ph.D. ("Dr. Warren"), is the William Patterson Timmie Professor of Human Genetics and Professor of Biochemistry and Professor of Pediatrics at Emory University as well as a past President of the American Society of Human Genetics. He personally supervises genetic research at Emory University and is also responsible for the Emory Genetics Laboratory. Dr. Warren is ready, willing, and able to being *BRCA1/2* genetic testing if the patents-in-suit were to be invalidated. Compl. ¶ 17.

Plaintiff Ellen Matloff, M. S. ("Ms. Matloff"), is Director of the Yale Cancer Genetic Counseling Program and a Research Scientist in the Department of Genetics at the Yale University School of Medicine. Ms. Matloff advises women on the desirability of obtaining an analysis of their genes to determine if the women have the genetic mutations that correlate with an increased risk of breast and/or ovarian cancer. Ms. Matloff also arranges for such genetic analysis and advises women on the significance of the results. As a result of the patents-in-suit, Ms. Matloff is currently required to utilize Myriad's testing services for analysis of *BRCA1/2*. If the patents-in-suit were to be invalidated, Ms. Matloff would immediately begin sending samples from women who are appropriate candidates for *BRCA* gene analysis to laboratories other than Myriad, such as the laboratories of Drs. Chung, Ledbetter, and Ostrer, for gene sequencing as well as large rearrangement testing. Matloff Decl. ¶¶ 1, 4, 10-15.

Plaintiff Elsa W. Reich, M.S. ("Ms. Reich"), is a Professor of Pediatrics in the Human Genetics Program at the NYU School of Medicine Department of Pediatrics, where she has served as a genetic counselor since 1974. Ms. Reich provides risk assessment and information to women and men about their risk of having a heritable form of cancer and advises them on the potential utility of obtaining an analysis of their genes to determine if they have genetic mutations that correlate with an increased risk of developing breast cancer, ovarian cancer, or other malignancies. The genes of most interest to be analyzed are the *BRCA1/2* genes. If a patient requests this testing, Ms. Reich sends samples to

Myriad and explains the results to the patient. If the patents-in-suit were to be invalidated, Ms. Reich would immediately begin sending samples, including ones previously tested by Myriad, to other laboratories, such as those of Drs. Chung, Ostrer, and Ledbetter for *BRCA1/2* testing. Reich Decl. ¶¶ 1-3, 7-9, 14-15.

Plaintiff Breast Cancer Action ("BCA") is a national organization of approximately 30,000 members based in San Francisco, California that works with researchers to encourage innovative approaches to unresolved issues in breast cancer. Members of Breast Cancer Action have had their *BRCA* genes analyzed or sought analysis to determine if they have genetic mutations that correlate with an increased risk of breast and/or ovarian cancer. In some instances, members have been unable to obtain testing at a laboratory of their choice or choose to be tested at a laboratory that would share data with researchers. In other instances, members have been unable to obtain genetic testing because of the high cost of the test. Members have also received ambiguous genetic test results from Myriad that show they have a genetic variant of uncertain significance, but have been unable to obtaining testing from a second laboratory. BCA staff and volunteers also provide information to members of the public about genetic analysis but have been unable to refer patients to labs other than Myriad. If the patents-in-suit were to be invalidated, BCA and its members would immediately begin utilizing other alternatives to Myriad's *BRCA1/2* testing services in addition to publicizing the existence of such alternatives, such as the laboratories of Drs. Chung and Ostrer.

Compl. ¶ 19; Brenner Decl. ¶¶ 2-3, 7, 9.

Plaintiff Boston Women's Health Book Collective ("BWHBC"), doing business as Our Bodies Ourselves ("OBOS"), is a women's health education, advocacy, and consulting organization that seeks to educate women about health, sexuality, and reproduction. OBOS staff provides information to members of the public about genetic analysis, but does not, as a result of the patents-in-suit, refer their readers to or publicize genetic testing services at, laboratories other than Myriad. BWHC also does not advocate for researchers and clinicians to perform *BRCA* testing as a result of the patents-in-suit. If the patents-in-suit were to be invalidated, BWHBC and OBOS are ready, willing, and able to provide information about testing options offered by labs other than Myriad and would directly benefit from any increased research on *BRCA1/2*. Compl. ¶ 20; Norsigian Decl. ¶¶ 2-3.

Plaintiff Lisbeth Ceriani ("Ms. Ceriani") is a 43-year-old single mother who was diagnosed with cancer in both breasts in May 2008. Ms. Ceriani's oncologist and genetic counselor recommended that she obtain *BRCA1/2* genetic testing to determine whether she should consider further surgery in order to reduce her risk of ovarian cancer. Because Myriad refused to accept Ms. Ceriani's insurance, however, her blood samples would not be processed unless she paid for the service out-of-pocket. Ms. Ceriani is unable to pay the full cost out-of-pocket and, to date, has not been tested and cannot determine her best medical course of action. Were Ms. Ceriani able to obtain genetic testing from Myriad, she would also want verification of the results of the *BRCA1/2* test before deciding whether to undergo removal of her ovaries. If the patents-in-suit were to be invalidated, Ms. Ceriani would pursue *BRCA1/2* genetic testing through laboratories other than Myriad, such as those of Drs. Chung and Ostrer. She would also seek verification of her *BRCA1/2* test results at a second lab. Ceriani Decl. ¶¶ 2-5, 7-11.

Plaintiff Runi Limary ("Ms. Limary") is a 32-year-old Asian-American woman who was diagnosed with aggressive breast cancer in November 2005. Following her diagnosis, she sought *BRCA1/2* genetic testing on the advice of her doctor. However, she was unable to be tested by Myriad until two years later, when she obtained insurance that provided coverage for the test. Her test results informed her that she possessed a "genetic variant of uncertain significance" in her *BRCA1* gene frequently identified in women of Asian descent and other racial minorities but whose significance as an indicator of predisposition to cancer was unclear. However, her test did not examine all known types of mutations in her *BRCA* genes, including known large rearrangements. Ms. Limary seeks additional resources for testing and research that could reveal the significance of her genetic variant, including whether it is correlated with an increased risk of breast or ovarian cancer, and could allow her to make an informed decision about her future medical treatment. If the patents-in-suit were to be invalidated, Ms. Limary would immediately pursue additional *BRCA1/2* genetic testing through other laboratories, such as those of Drs. Chung and Ostrer. Such testing would include additional analysis to determine the significance of her *BRCA1* variant of unknown significance. Limary Decl. ¶¶ 2-6, 8-9.

Plaintiff Genae Girard ("Ms. Girard") is a 39-year-old woman who was diagnosed with breast cancer in 2006. Shortly after her diagnosis, she obtained *BRCA1/2* genetic testing from Myriad and tested positive for a deleterious mutation on the *BRCA2* gene. She sought, but was unable to obtain a second opinion confirming the test result before making any decisions concerning prophylactic bilateral breast surgery and ovarian surgery. IF the patents-in-suit were to be invalidated, Ms. Girard would immediately pursue *BRCA1/2* genetic testing through other laboratories, such as those of Drs. Chung and Ostrer. Girard Decl. ¶¶ 2-5, 10.

Plaintiff Patrice Fortune ("Ms. Fortune") is a 48-year-old woman who was diagnosed with breast cancer in February 2009. Because Ms. Fortune has a family history of breast cancer, her genetic counselor and oncologist advised her to seek *BRCA1/2* genetic testing. However, as a result of incomplete coverage for Myriad's test by Ms. Fortune's health insurance, Ms. Fortune would be required by Myriad to pay the full out-of-pocket cost for her genetic testing. Because Ms. Fortune currently works in unpaid positions while receiving treatment for her cancer, she cannot afford the cost of Myriad's genetic testing. If the patents-in-suit were to be invalidated, Ms. Fortune would immediately seek testing through other laboratories, such as those of Drs. Chung and Ostrer, in addition to seeking a second opinion by another lab before making any major decisions about her treatment. Fortune Decl. ¶¶ 2-5, 8.

Plaintiff Vicky Thomason ("Ms. Thomason") is a 52-year-old woman who was diagnosed with ovarian cancer in 2006. She obtained *BRCA1/2* genetic testing from Myriad in 2007 at the advice of her doctor and genetic counselor and was found to be negative for mutations covered by that test. However, in light of her family history of cancer, her genetic counselor advised her that she was an appropriate candidate for the additional *BRCA1/2* genetic testing offered by Myriad that looks for large genetic rearrangements that are not detected by Myriad's standard genetic test. However, Ms. Thomason's insurance will not cover the entire cost of Myriad's additional test, and Ms. Thomason is unable to afford the extra cost. If the patents-in-suit were to be invalidated, Ms. Thomason would immediately seek *BRCA1/2* testing, including the large rearrangement testing that she currently cannot afford, through other laboratories, such as those of Drs. Chung and Ostrer. Thomason Decl. ¶¶ 2-6, 8, 10.

Plaintiff Kathleen Raker ("Ms. Raker") is a 42-year-old woman whose mother and maternal grandmother died from breast cancer. She obtained *BRCA1/2* genetic testing from Myriad in 2007 and was found to be negative for mutations covered by that test. However, her genetic counselor advised her that she could still face hereditary risks for breast cancer due to a mutation in her *BRCA* genes that could not be detected by Myriad's standard test, but might be detected by Myriad's test for large rearrangements. Ms. Raker is unable to afford the cost of Myriad's additional testing and, to date, has not received this testing. Without those results, she cannot determine the risk of cancer she or her children face. If the patents-in-suit were to be invalidated, Ms. Raker would immediately pursue *BRCA1/2* testing through other laboratories, such as those of Drs. Chung and Ostrer. Raker Decl. ¶¶ 2-3, 5-7, 8-9, 11-12.

B. The Defendants

The USPTO is an agency of the Commerce Department of the United States. Compl. ¶ 27. The Plaintiffs assert only their claims' for constitutional violations against the USPTO.

Myriad is a for-profit corporation located in Salt Lake City, Utah, doing business throughout the United States. Myriad Genetics is a co-owner of one of the patents-in-suit and holds the exclusive licenses for the remaining ones. It is currently the sole clinical provider of full sequencing of the BRCA genes in the United States. Compl. ¶ 28.

The Directors are directors of the UURF, a not-for-profit corporation located in Salt Lake City, Utah, that the Plaintiffs allege is operated, supervised, and/or controlled by the University of Utah. The UURF is an owner or part-owner of all of the patents-in-suit.[4] Compl. ¶ 29.

C. *BRCA1* and *BRCA2*

The human body is composed of cells. Contained in the nucleus of each cell are the genes that serve as the blueprints used by the body to create the proteins and gene products required for its function. Human genes are composed of unique combinations of four DNA[5] nucleotides (i.e., bases) referred to by the letters A, T, C, and G. The sequence of each gene reflects the string of hundreds or thousands of A, T, C, and G nucleotides that make up the gene. Each gene has a normal, or "wild-type" sequence of nucleotides. Compl. ¶¶ 33, 35, 36.

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[4] The United States of America, represented by the Secretary of Health and Human Services, is an additional owner of the '001, '441, '897, and '282 patents. Endo Recherche, Inc., of Quebec, Canada, HSC Research and Development Limited Partnership of Toronto, Canada, and the Trustees of the University of Pennsylvania are additional owners of the '492 and '857 patents. Compl. ¶ 30.

The sequence of any given human gene varies in nature from one person to another and frequently varies from the "wild-type" sequence. Some of the variations, referred to as "mutations" or "variants," can impact the body's ability to create proteins necessary for sound health. These mutations can include individual nucleotide substitutions (e.g., a T where G would normally appear in a gene), individual nucleotide deletions (e.g. a G being deleted altogether from a particular location in a gene), or much larger variations (e.g. a section of a gene containing numerous nucleotides is deleted or displaced). Mutations can be inherited from an individual's parents as well as be acquired during an individual's lifetime. Id.

To find out if the nucleotide sequence of a person's gene differs from the normal, or "wild-type" nucleotide sequence for the gene, a genetic researcher or clinician can sequence the person's gene to determine its nucleotide sequence. Once the sequence of the gene has been obtained, the researcher or clinician can examine the entire sequence to see if the A, T, C, and Gs encode a healthy sequence, a sequence with mutations known to be associated with cancer, or a sequence with one or more variants of uncertain significance. Alternatively, the researcher or clinician can sequence and examine a small section of the gene where a particular mutation or variant is known to occur. The methods by which researchers or clinicians identify the sequence of either the whole gene or any part thereof are not patented in the claims at issue here and are well known in the field. Compl. ¶ 36.

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[5] DNA, which stands for deoxyribonucleic acid, is a chemical compound made by the body. Compl. ¶ 34.

In the 1990s, a number of genetic researchers around the world began looking for a human gene that correlated with an increased risk of breast and/or ovarian cancer. Many of those researchers, including the researchers who ultimately formed Myriad, were funded, at least in part, by the federal government. Researchers, using techniques widely available in the profession, determined in 1990 that one gene that correlated with an increased risk of breast and/or ovarian cancer was located in the body on chromosome 17. Another research team that was eventually associated with Myriad, using techniques widely available in the profession, sequenced the precise gene, which was named *BRCA1* because of its correlation with breast cancer susceptibility. These researchers subsequently formed Myriad. Myriad sought, and ultimately obtained, several patents on this human *BRCA1* gene. Researchers also began looking for other genes similar to *BRCA1*, and Myriad, using techniques widely available in the profession, subsequently identified *BRCA2* and obtained a series of patents over the human *BRCA2* gene. As a result, Myriad holds, either through ownership or exclusive license, numerous patents relating to the human *BRCA1* and *BRCA2* genes.

Compl. ¶¶ 41-45.

The patents for *BRCA1/2* were granted by the USPTO pursuant to a formal written policy that provides that naturally occurring genes can be patented if they are "isolated from their natural state and purified." Compl. ¶ 50. According to USPTO policy, an "isolated and purified" gene includes one that is simply removed from the body and separated from the other contents of the cell. Compl. ¶ 51. However, the information dictated by the gene is identical whether it is inside or outside of the body, and an "isolated and purified" human gene performs the same function as the human gene in a person's body. Id. USPTO policy also permits patenting of comparisons or correlations created by nature, but identified by a patent holder. Compl. ¶ 53.

Everyone carries the *BRCA1* and *BRCA2* genes, but the sequence of each person's *BRCA* genes can differ. Compl. ¶ 37. Certain mutations in the genes are correlated with an increased risk of breast and/or ovarian cancer and may also be associated with other cancers, such as prostate and pancreatic cancers. Id. Women with these mutations have an approximately 40-85% lifetime risk of developing breast cancer. Compl. ¶ 39. Approximately 5-10% of women who develop breast cancer are likely to have a mutation in their *BRCA1* or *BRCA2* genes predisposing them to breast cancer and which they inherited from their parents. Compl. ¶ 38.

A *BRCA1/2* genetic test result that is positive for one of these mutations can have a substantial impact on a woman's medical decisions and health. Many women will obtain earlier and more vigilant screening for breast and/or ovarian cancers, and some women may choose to have prophylactic surgery to remove their breasts and/or ovaries in order to reduce the risk of future cancers. Compl. ¶ 40.

D. Enforcement of the Patents-in-Suit

In the late 1990s, the GDL at the University of Pennsylvania was engaged in providing *BRCA1* genetic testing services to women. Kazazian Decl. ¶ 4. Around this time, Dr. Kazazian, one of the co-Directors of the GDL, met with Dr. Mark Skolnick ("Dr. Skolnick"), the Chief Science Officer at Myriad. During the meeting, Dr. Skolnick informed Dr. Kazazian that Myriad planned to stop the *BRCA1* and *BRCA2* testing being done by the GDL. Kazazian Decl. ¶ 6. Shortly thereafter, on or about May 29, 1998, Dr. Kazazian received a letter from William A. Hockett, Director of Corporate Communications for Myriad which asserted that Myriad is "the patent holder for the *BRCA1* gene" covering, among other things "composition of matter covering the *BRCA1* gene [and] any fragments of the *BRCA1* gene." Ganguly Decl. ¶ 5. The letter further offered the University a collaboration license of very limited scope. Id.

On or about August 26, 1998, Dr. Kazazian received a cease-and-desist letter from George A. Riley of O'Melveny & Myers, LLP, asserting that the Dr. Kazazian's commercial testing activities infringed the patents-in-suit and demanding that he cease "all infringing testing activity." Ganguly Decl. ¶ 6.

On or about June 10, 1999, the University of

Pennsylvania general counsel, Robert Terrell, received a letter from Christopher Wright, Myriad's General Counsel, asserting that Dr. Kazazian's *BRCA* testing activities infringed the patents-in-suit and demanding that the university cease all such commercial genetic testing services. Ganguly Decl. ¶ 7. In a subsequent letter to the University dated September 22, 1999, Myriad reiterated its belief that the genetic testing activities being performed at the GDL infringed the patents-in-suit and repeated its demand that such activities cease. Ganguly Decl. ¶ 9.

As a result of these letters, the University of Pennsylvania advised Drs. Kazazian and Ganguly to discontinue their *BRCA1/2* testing, which they did. Kazazian Decl. ¶ 7; Ganguly Decl. ¶ 10.

During this same period, Dr. Harry Ostrer was sending patient samples to Dr. Kazazian for *BRCA1/2* related genetic screening. Ostrer Decl. ¶ 5. On May 21, 1998, Dr. Ostrer also received a letter from William Hocket similar to that sent to Dr. Kazazian. The letter notified Dr. Ostrer of Myriad's patents and offered him a license for *BRCA1/2*-related genetic testing. Ostrer Decl. ¶ 7. Because of the narrow scope of the proposed license, Dr. Ostrer did not enter into a licensing agreement with Myriad. Id.

On or about September 15, 1998, Gregory Critchfield, the President of Myriad, sent a letter to Dr. Susan Nayfield of the National Cancer Institute ("NCI"). Ganguly Decl. Ex. 7. The letter assured Dr. Nayfield that Myriad would not interfere with research activities supported by the NCI in any way, but noted that Myriad had, over the past several months, sent several laboratories engaged in the "commercial testing" of the *BRCA1* gene draft license agreements defining the conditions under which those laboratories would be allowed to conduct commercial genetic testing. Id.

On or about September 2, 1999, a Myriad representative sent a letter to a Georgetown laboratory demanding that it no longer sent genetic samples to the GDL for testing because such testing infringed the patents-in-suit. Ganguly Decl. ¶ 13. As a result of the letter, Georgetown stopped sending samples to the GDL for *BRCA1/2* screening. Id.

In December 2000, the director of the Yale DNA Diagnostics Laboratory (the "YDL") received a letter from Myriad directing that the YDL cease the *BRCA1/2* genetic testing that was being conducted in the laboratory because the testing allegedly infringed the patents-in-suit. Matloff Decl. ¶ 7. Following receipt of the letter, the laboratory ceased offering such genetic testing. Id.

In 2005, Ms. Matloff telephoned Myriad to inquire whether it was permissible for the YDL to perform genetic screening of the *BRCA* genes that looked for large rearrangement mutations. Matloff Decl. ¶ 8. Several scientific studies had demonstrated that Myriad's full sequencing test missed large rearrangements that are also correlated with cancer risk. Myriad informed Ms. Matloff that this large rearrangement testing could not be done by the Yale laboratory because it would infringe the patents-in-suit. Id.

Myriad has also engaged in litigation to assert its rights under the patents-in-suit. In 1997 and 1998, Myriad filed suit against Oncormed, a company offering competing *BRCA1/2* genetic testing. See Myriad Genetics v. Oncormed, 2:97-cv-922 (D. Utah); Myriad Genetics v. Oncormed, 2:98-cv-35 (D. Utah). In November 1998, Myriad sued the University of Pennsylvania for infringing its *BRCA* patents. See Myriad Genetics v. Univ. of Pennsylvania, 2:98-cv-829 (D. Utah). Although the lawsuit was dismissed after the University agreed to cease its *BRCA* testing, the dismissal was "without prejudice." See 2:98-cv-829 (D. Utah) (docket entry 3).

As a result of these efforts, it is widely understood within the research community that Myriad has taken the position that any *BRCA1/2* related activity infringes its patents and that Myriad will assert its patent rights against parties engaged in such activity. See, Ostrer Decl. ¶¶ 5-6; Chung Decl. ¶ 15; Hubbard Decl. ¶ 7; Kant Decl. ¶ 4; Matloff Decl. ¶¶ 7-9; Reich Decl. ¶ 5; see also Mildred K. Cho, et al., Effects of Patents and License on the Provision of Genetic Testing Services, 5 J. Molecular Diagnostics 3 (2003) (reporting that nine clinical genetic testing laboratories ceased *BRCA1/2* testing as a result of Myriad's patents).

III. THE PARTIES' CONTENTIONS

The Plaintiffs challenge the validity of claims 1, 2, 5, 6, 7, and 20 of patent 5,747,282 (the "'282 patent") ; claims 1, 6, and 7 of patent 5,837,492 (the "'492 patent"); claim 1 of patent 5,693,473 (the "'473 patent"); claim 1 of patent 5,709,999 (the "'999 patent"); claim 1 of patent 5,710,001 (the "'001 patent"); claim 1 of patent 5,753,441 (the "'441 patent"); and claims 1 and 2 of patent 6,033,857 (the "'857 patent").

The Plaintiffs divide the claims-in-suit into four categories. The first category of claims, which include claims 1, 2, 5, and 6 of the '282 patent and claim 1 of the '492 patent, cover isolated, non-mutated forms of *BRCA1* and *BRCA2* as well as fragments of *BRCA1* of 15 nucleotides or more. The second category of claims, which includes claim 1 of the '473 patent, claim 7 of the '282 patent and claims 6 and 7 of the '492 patent, cover isolated forms of *BRCA1* and *BRCA2* that contain mutations that may or may not have any correlation with an increased risk of breast and ovarian cancer. The third category of claims, comprised of claim 1 of the '999 patent, covers any method of analyzing an individual's *BRCA1* gene to determine whether the individual's gene contains an inherited mutation. The fourth category of claims, which includes claim 1 of the '001 patent, claim 1 of the '441 patent, and claims 1 and 2 of the '857 patent, covers comparison of a patients' *BRCA1* and *BRCA2* gene sequences with the normal *BRCA1* and *BRCA2* gene sequences to determine whether there are differences that would indicate a genetic predisposition to breast cancer. Claim 20 of the '282 patent, which the Plaintiffs include in this fourth category of claims, covers a method of examining the growth of cells containing a mutated form of *BRCA1* following their treatment with a potential therapeutic compound. None of the claims in the fourth category of claims are limited to "isolated" DNA.

The Plaintiffs allege that because human genes are products of nature, laws of nature, and/or natural phenomena, and abstract ideas or basic human knowledge or thought, the claims-in-suit are invalid for violating Article 1, section 8, clause 8 of the United States Constitution, the First and Fourteenth Amendments to the Constitution, and 35 U.S.C. § 101 of the patent statute. Compl. ¶ 52, 54.

According to the Plaintiffs, these genes exist as naturally occurring products of nature, and Myriad did not invent, create, or in any way construct or engineer the genes. Rather, Myriad located them in nature and described their informational content as it exists and functions in nature. According to the Plaintiffs, Myriad did not invent, create, or in any way construct the differences that may be found when a patient's *BRCA1/2* gene sequences are compared to the normal *BRCA1/2* gene sequences or the correlations between certain mutations in *BRCA1/2* and an increased risk of breast and/or ovarian cancer. Compl. ¶¶ 46, 48.

Myriad currently offers two types of tests: the Comprehensive BRACAnalysis Test and the BRACAnalysis Rearrangement Test ("BART"). The Comprehensive BRACAnalysis Test costs over $3000; BART costs approximately $600, although Myriad will offer BART testing for free to some women who meet certain criteria. Compl. ¶ 92, 94. Although Myriad's tests examine many mutations known to correlate with a predisposition to breast and/or ovarian cancer, they do not look for all mutations known to correlate with breast and/or ovarian cancer. Ledbetter Decl. ¶ 16. The Plaintiffs allege that Myriad's patents on *BRCA1/2* have allowed it to bar any other entity from conducting genetic testing on the *BRCA* genes despite the ability of other clinical laboratories, such as the laboratories of Drs. Chung, Ostrer, and Ledbetter, to do so and the desire of patients, such as Ms. Limary and Ms. Girard, to seek such alternative testing. Compl. ¶ 84. As a result, any person seeking testing of their *BRCA1/2* genes is required to utilize Myriad's tests. Compl. ¶ 90.

According to the Plaintiffs, Myriad also has the ability to prevent researchers from conducing any research examining the *BRCA* genes. Compl. ¶ 96. Myriad has permitted some scientists to conduct pure research on *BRCA1/2,* but the Plaintiffs allege that Myriad has no official policy permitting such research and has not publicized its willingness to allow such research. Compl. ¶ 97. The Plaintiffs allege that the patents on the *BRCA* gene sequences deny researchers access to genomic information which, unlike other patented inventions, cannot be "invented around" or built upon to foster scientific progress. Commpl. ¶ 88. As a result, researchers are chilled from engaging in research on *BRCA1/2* as well as research on other genes that may interact with *BRCA1/2*. Compl. ¶ 98. Included in such activities would be the development of new tests for breast and/or ovarian cancer that might be linked to *BRCA1/2* . The Plaintiffs assert that this infringes on quality medical practice and compromises quality assurance and improvement of testing. Compl. ¶ 101; Ledbetter Decl. ¶ 23.

The Defendants have moved to dismiss the claims against them pursuant to Fed. R. Civ. P 12(b) (1) on the grounds that the Court lacks subject matter jurisdiction over Plaintiffs' claims against the USPTO and that the Plaintiffs lack standing to bring this declaratory judgment action. The Defendants have also moved to dismiss the claims against the

UURF Directors pursuant to Fed. R. Civ. P. 12(b) (2) on the grounds that the Court lacks personal jurisdiction over the Directors. Finally, the Defendants move to dismiss the constitutional claims pursuant to Fed. R. Civ. P. 12(b) (6) for failure to sufficiently plead a claim.

IV. THERE IS SUBJECT MATTER JURISDICTION OVER THE CLAIMS AGAINST THE USPTO

The USPTO has moved to dismiss the Complaint, pursuant to Rule 12(b)(l), on the grounds that the Court lacks subject matter jurisdiction over the Plaintiffs' claims. A claim is "properly dismissed for lack of subject matter jurisdiction under Rule 12(b)(l) when the district court lacks the statutory or constitutional power to adjudicate it." Makarova v. United States, 201 F.3d 110, 113 (2d Cir. 2000). "When jurisdiction is challenged, the plaintiff 'bears the burden of showing by a preponderance of the evidence that subject matter jurisdiction exists.'" Arar v. Ashcroft, 532 F.3d 157, 168 (2d Cir. 2008) (quoting APWU v. Potter, 343 F.3d 619, 623 (2d Cir. 2003)). "[J]urisdiction must be shown affirmatively, and that showing is not made by drawing from the pleadings inferences favorable to the party asserting it." Shipping Fin. Servs. Corp. v. Drakos, 140 F.3d 129, 131 (2d Cir. 1998) (citation omitted). As such, the Court may rely on evidence outside the pleadings, including declarations submitted in support of the motion and the records attached to these declarations. See Makarova, 201 F.3d at 113 ("In resolving a motion to dismiss . . . under Rule 12(b)(l), a district court . . . may refer to evidence outside the pleadings. ").

The Plaintiffs premise their assertion of subject matter jurisdiction on 28 U.S.C. §§ 1331 & 1338(a).[6] 28 U.S.C. § 1331 vests the district courts with subject matter jurisdiction for "all civil actions arising under the Constitution." The USPTO, however, asserts that the Court lacks subject matter jurisdiction over Plaintiffs' claims against them in light of the "comprehensive scheme Congress established to govern patent grants."[7] Hitachi Metals, Ltd. v. Quigg, 776 F. Supp. 3, 7 (D.D.C. 1991). According to the USPTO, the existence of this comprehensive statutory scheme reflects Congress' intention to preclude judicial challenges of the type brought by the Plaintiffs.

The cases cited by the USPTO, however, involved claims alleging statutory violations for which the Patent Act provided a remedy. The issue before the courts, then, was whether the existence of a comprehensive statutory scheme that addressed the alleged statutory violation precluded the right to also seek judicial review of the alleged violations. See Syntex (U.S.A.), Inc. v. U.S. Patent & Trademark Office, 883 F.2d 1570, 1572-74 (Fed. Cir. 1989) (concluding remedy provided by patent statute for alleged statutory violations precluded private judicial remedy for those claims);[8] Hallmark Cards, Inc. v. Lehman, 959 F. Supp. 539, 543 (D.D.C. 1997) (concluding Congress' statutory framework providing means to challenge issuance of Certificates of Correction "implicitly preclude[d]" a right to judicial relief); Hitachi Metals, 776 F. Supp. at 7-8 (finding statutory scheme for administrative and judicial review of patent reissue decisions precluded third-party judicial challenges to reissue process).

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[6] Although Plaintiffs also cite 28 U.S.C. § 2201 as a basis for jurisdiction, "[i]t is settled law that the Declaratory Judgment Act, 28 U.S.C. § 2201 (1994), does not enlarge the jurisdiction of the federal courts . and that a declaratory judgment action must therefore have an independent basis for subject matter jurisdiction." Concerned Citizens of Cohocton Valley, Inc. v. N.Y. State Dep't of Envtl. Conservation, 127 F.3d 201, 206 (2d Cir. 1997) (citing Skelly Oil Co. v. Phillips Petroleum Co., 339 U.S. 667, 671 (1950)).

[7] The USPTO also argues that sovereign immunity serves to bar this action. Courts, however, routinely entertain actions against federal agencies alleging violations of the Constitution. See, e.g., Reno v. ACLU, 521 U.S. 844 (1997). As Plaintiffs note in their Complaint, the only claims raised against the USPTO are of a constitutional nature. Compl. ¶ 27.

In Bush v. Lucas, 462 U.S. 367 (1983), cited by the USPTO, the Supreme Court considered whether an employee subjected to adverse employment action as a result of his criticism of the federal agency employing him could maintain a suit against the agency for violation of his First Amendment rights. Id. at 369-72. Noting that "the ultimate question on the merits . . . may appropriately be characterized as one of 'federal personnel policy,'" id. at 380-81, the Court went on to describe Congress' "repeated consideration of the conflicting interests involved in providing job security, protecting the right to speak freely, and maintaining discipline and efficiency in the federal workforce." Id. at 385. The result, the Court concluded, was an "elaborate, comprehensive scheme" within which "Constitutional challenges to agency action, such as First Amendment claims raised by petitioner, are fully cognizable." Id. As a result, the Court was presented with a question "quite different from the typical remedial issue confronted by a common-law court" since the issue was not whether a judicial remedy should be created where none existed, but rather whether a judicial remedy should be created where a plaintiff was merely dissatisfied by the statutory remedy Congress provided for his alleged wrong. Id. at 388.

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[8] The Syntex opinion noted in passing that the plaintiff had pled a violation of the 5th Amendment, but included no discussion concerning the claim in its analysis of subject matter jurisdiction.

While the USPTO notes the existence of a comprehensive scheme to redress violations of the Patent Act, it cites to no comparable statutory scheme providing a remedy for persons who complain about the constitutionality of patents issued by the USPTO and/or the policies and practices of the USPTO. See Block v. Cmty. Nutrition Inst., 467 U.S. 340, 349 (1984) ("[W]hen a statute provides a detailed mechanism for judicial consideration of particular issues at the behest of particular persons, judicial review of those issues at the behest of other persons may be found to be impliedly precluded." (emphasis added)); see generally Marbury v. Madison, 5 U.S. 137 (1803). In such circumstances, the Supreme Court has held that Congress did not intend to preclude enforcement of federal rights through private actions. See Wright v. Roanoke, 479 U.S. 418, 427-28 (1987) (citing absence of statutorily defined private judicial remedy for alleged violation of federal housing law as evidence that Congress did not intend to foreclose private right of action). Indeed, even when Congress has created a statutory remedy, if that remedy is not coextensive with the remedy provided by the Constitution, plaintiffs may still bring a separate action to enforce the

Constitution. See Fitzgerald v. Barnstable Sch. Comm., __U.S.__, 129 S. Ct. 788, 796-978 (2009).

The novel circumstances presented by this action against the USPTO, the absence of any remedy provided in the Patent Act, and the important constitutional rights the Plaintiffs seek to vindicate establish subject matter jurisdiction over the Plaintiffs' claim against the USPTO.[9] See, e.g., Reno v. ACLU, 521 U.S. 844 (1997); Mace v. Skinner, 34 F.3d 854, 859-60 (9th Cir. 1994).

V. THERE IS STANDING

A. The Plaintiffs Have Standing to Sue the USPTO for Constitutional Violations

The "judicial power . . . defined by Art. III is not an unconditioned authority to determine the constitutionality of legislative or executive acts" but, rather, is limited to the resolution of "cases" and "controversies." Valley Forge Christian Coll. v. Ams. United for Separation of Church & State, Inc., 454 U.S. 464, 471 (1982); Lujan v. Defenders of Wildlife, 504 U.S. 555, 559-60 (1992). An "essential and unchanging part" of that limitation is the doctrine of standing. Lujan, 504 U.S. at 560. Indeed, "[tlhe Art. III doctrine that requires a litigant to have 'standing' to invoke the power of a federal court is perhaps the most important of these doctrines." Allen v. Wright, 468 U.S. 737, 750 (1984). "At an irreducible minimum, Art. III requires the party who invokes the court's authority to show (1) that he personally has suffered some actual or threatened injury as a result of the putatively illegal conduct of the defendant, that (2) the injury fairly can be traced to the challenged action, and (3) is likely to be redressed by a favorable decision." Valley Forge, 454 U.S. at 472 (internal citations omitted).[10]

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[9] Although the USPTO suggests that finding subject matter jurisdiction over Plaintiffs' constitutional claims would open the gates to a flood of challenges to patents based on alleged constitutional violations, it is difficult to see how a colorable claim for constitutional violations could arise out of patents for more commonly patented inventions, such as computer chips or carburetors.

Beyond these constitutional requirements, a plaintiff must also satisfy certain prudential standing requirements, based on the principle that the judiciary should "avoid deciding questions of broad social import where no individual rights would be vindicated." Phillips Petroleum Co. v. Shutts, 472 U.S. 797, 804 (1985). Prudential standing requires, inter alia, that a party "assert his own legal interests rather than those of third parties," id. at 804, and that a claim must not be a "generalized grievance" shared in by all or a large class of citizens, Warth v. Seldin, 422 U.S. 490, 499 (1975). Prudential standing also addresses whether "the constitutional or statutory provision on which [a plaintiff's] claim rests properly can be understood as granting persons in the plaintiff's position a right to judicial relief."

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[10] The USPTO's challenge to Plaintiffs' standing is intertwined with its challenge to Plaintiffs' subject matter jurisdiction. See Syntex, 882 F.2d at 1573 ("The standing and reviewability inquiries tend to merge. A plaintiff cannot claim standing based on violation of an asserted personal statutorily-created procedural right when Congress intended to grant that plaintiff no such right." (quoting Banzhaf v. Smith, 737 F.2d 1167, 1170 n.* (D.C. Cir. 1984))).

See id. at 499-500. Thus, the litigant's complaint must fall within the "zone of interests to be protected or regulated by the statute or constitutional guarantee in question." Valley Forge, 454 U.S. at 475.

The Defendants allege that it is well established that third parties do not have standing to challenge the USPTO's issuance of a patent. The authorities cited by the USPTO, however, address a party's standing to bring claims for statutory violations and establish only that the existence of a comprehensive framework within the Patent Act designed to address certain statutory violations may demonstrate Congressional intent to foreclose a judicial remedy for those violations. See Syntex, 882 F.2d at 1572-74; Hitachi Metals, 776 F. Supp. at 7-8; Godtfredsen v. Banner, 503 F. Supp. 642, 644-45 (D.D.C. 1980) (finding statutory remedies for claims of examiner error during interference proceedings precluded judicial review of the proceedings prior to the exhaustion of administrative remedies).[11] As discussed supra in Section IV, these cases do not, as the USPTO suggests, establish that the remedial scheme provided by the Patent Act for statutory violations divests the Plaintiffs of standing to assert constitutional claims for which the Patent Act provides no remedy.

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[11] Animal Legal Defense Fund, 932 F. 2d 920 (Fed. Cir. 1991), cited by the USPTO, did not involve allegations of constitutional violations. Moreover, the court's analysis of standing turned on the specific APA provisions involved and was, in substance, a finding that no legally cognizable right was violated. See id. at 929-30. The court's holding also turned on the fact that no patents on animals had been granted and therefore any harm that might occur in the future from such patents was speculative. Id. at 933. The same cannot be said here, where patents over *BRCA1/2* have already been granted and have been used to present Plaintiffs from engaging in clinical analysis of the *BRCA1/2* genes, from informing women about testing options other than by Myriad, and from obtaining genetic testing or second opinions. Plaintiffs alleged harms are

The USPTO also argues that the Plaintiffs do not have standing because the injuries alleged are not "fairly traceable" to the USPTO's allegedly improper conduct. The "fairly traceable" requirement "examines the causal connection between the assertedly unlawful conduct and the alleged injury." Allen, 468 U.S. at 753 n.19. While the USPTO is correct that Myriad's refusal to license its patent broadly contributes to Plaintiffs' alleged injuries, the patents were issued by the USPTO, in accordance with its policies and practices. It is those policies and practices that the Plaintiffs allege are unconstitutional. The injury alleged is therefore "fairly traceable" to the USPTO .

Finally, the USPTO argues that Plaintiffs' claim against it fails to meet the redressibility requirement, which "examines the causal connection between the alleged injury and the judicial relief requested." Allen, 468 U.S. at 753 n.9. The Plaintiffs ask the Court to enjoin the Defendants from taking any actions to enforce the challenged claims in Myriad's patents. Fairly included in this prayer for relief is a request that the Court declare unconstitutional the USPTO's policies and practices with respect to the challenged claims and similar

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therefore not the type of speculative harms at issue in Animal Legal Defense Fund.

classes of claims. Granting Plaintiffs' request for relief would serve to render the claims-at-issue definitionally invalid. As a result, the Plaintiffs would be allowed to engage in conduct currently prohibited by Myriad's patents, and the alleged injuries would be redressed.

B. The Plaintiffs Have Established Standing to Sue Myriad and the Directors

Article III limits federal jurisdiction to disputes involving an actual "case or controversy," and not merely "a difference or dispute of a hypothetical or abstract character." Aetna Life Ins. Co. v. Haworth, 300 U.S. 227, 240 (1937). As the Supreme Court has recently observed, there exists no bright-line rule for determining whether an action satisfies the case or controversy requirement. MedImmune, Inc. v. Genentech, Inc., 549 U.S. 118, 127 (2007). Rather, "[t]he difference between an abstract question and a 'controversy' contemplated by the Declaratory Judgment Act is necessarily one of degree, and it would be difficult, if it would be possible, to fashion a precise test for determining in every case whether there is such a controversy." Md. Cas. Co.. v. Pac. Coal & Oil Co., 312 U.S. 270, 273 (1941). Consequently, "the analysis must be calibrated to the particular facts of each case." Cat Tech LLC v. TubMasters, Inc., 528 F.3d 871, 879 (Fed. Cir. 2008).

"Whether an actual case or controversy exists so that a district court may entertain an action for a declaratory judgment of non-infringement and/or invalidity is governed by Federal Circuit law." MedImmune, Inc. v. Centocor, Inc., 409 F.3d 1376, 1378 (Fed. Cir. 2005) (citations omitted), rev'd on other grounds, 549 U.S. 118 (2007). "The purpose of the Declaratory Judgment Act . . . in patent cases is to provide the allegedly infringing party relief from uncertainty and delay regarding its legal rights." Goodyear Tire & Rubber Co. v. Releasomers, Inc., 824 F.2d 953, 956 (Fed. Cir. 1987). As the Federal Circuit has explained:

> [A] patent owner . . . attempts extrajudicial enforcement with scare-the-customer-and-run tactics that infect the competitive environment of the business community with uncertainty and insecurity . . . . Before the Act, competitors . . . were rendered helpless and immobile so long as the patent owner refused to grasp the nettle and sue. After the Act, those competitors were no longer restricted to an in terrorem choice between the incurrence of a growing potential liability for patent infringement and abandonment of their enterprises; they could clear the air by suing for a judgment that would settle the conflict of interests.

Elecs. for Imaging, Inc. v. Coyle, 394 F.3d 1341, 1346 (Fed. Cir. 2005) (quoting Arrowhead Indus. Water, Inc. v. Ecolochem, Inc., 846 F.2d 731, 735 (Fed. Cir. 1988), overruled on other grounds by MedImmune, 549 U.S. 118).

The Federal Circuit's jurisprudence governing a party's standing to seek a declaratory judgment of patent invalidity was recently revised by the

Supreme Court in MedImmune, 549 U.S. 118. There, the Supreme Court considered whether the licensee of a patent had standing to seek a judgment declaring the underlying patent invalid, unenforceable, or not infringed without first breaching or terminating the license agreement. Id. at 137. In concluding that subject matter jurisdiction existed over the plaintiff's declaratory judgment claim, the Supreme Court rejected the Federal Circuit's "reasonable apprehension of suit" test as conflicting with the Court's precedent. Id. at 132 n.11; see also Revolution Eyewear, Inc. v. Aspex Eyewear, Inc., 556 F.3d 1294, 1297 (Fed Cir. 2009) (observing that "the Federal Circuit's requirements, specific to patent cases, that there be both a threat or other action by the patentee sufficient to create a reasonable apprehension of infringement suit, and present activity that could constitute infringement or concrete steps taken with the intent to conduct such activity, were more rigorous than warranted by the principle and purpose of declaratory actions.").[12] Instead, the Court held that the jurisdictional analysis was properly based on an examination of "all the circumstances." MedImmune, 549 U.S. at 127.

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[12] Under the "reasonable apprehension of suit" test, determining whether a party seeking a declaratory judgment of invalidity possessed the necessary standing required examining (1) "whether the declaratory judgment plaintiff actually produced or was prepared to produce an infringing product;" and (2) "whether conduct by the patentee had created on the part of the declaratory judgment plaintiff a reasonable apprehension that the patentee would file suit of the allegedly infringing activity continued." Sony Elecs. Inc v. Guardian Media Techs., Ltd., 497 F.3d 1271, 1283 (Fed. Cir. 2007).

Under the "all the circumstances" test, "the question in each case is whether the facts alleged, under all the circumstances, show that there is a substantial controversy, between the parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment." Id. at 127 (quoting Md. Cas. Co., 312 U.S. at 273). This "more lenient legal standard facilitates or enhances the availability of declaratory judgment jurisdiction in patent cases," and, accordingly, there is now an "ease of achieving declaratory judgment jurisdiction." Micron Tech. v. Mosaid Techs. Inc., 518 F.3d 897, 902 (Fed. Cir. 2008). Courts in this district have likewise recognized that since MedImmune, "the trend is to find an actual controversy, at least where the declaratory judgment plaintiff's product arguably practices a patent and the patentee has given some indication it will enforce its rights." Diamonds.net LLC v. IDEX Online, Ltd., 590 F. Supp. 2d 593, 597-98 (S.D.N.Y. 2008).

Although MedImmune did not define the precise contours of the "all the circumstances" test, guidance is provided by other courts' standing analysis. First, there must be some affirmative act by the defendant relating to enforcement of its patent rights. See, e.g., Prasco, LLC v. Medicis Pharm. Corp., 537 F.3d 1329, 1338-39 (Fed. Cir. 2008); SanDisk Corp. v. STMicroelectronics, Inc., 480 F. 3d 1372, 1380-81 (Fed. Cir. 2007) ("[J]urisdiction generally will not arise merely on the basis that a party learns of the existence of a patent owned by another or even perceives such a patent to pose a risk of infringement, without some affirmative act by the patentee."). Second, the declaratory judgment plaintiff must have undertaken "meaningful preparation to conduct potentially infringing activity." Cat Tech LLC, 528 F.3d at 880. This inquiry ensures that a party does not seek a declaratory judgment "merely because it would like an advisory opinion on whether it would be liable for patent infringement if it were to initiate some merely contemplated activity." Arrowhead, 846 F.2d at 736 (citations omitted). Whether there exists "sufficient 'preparation' is a question of degree to be resolved on a case-by-case basis." Id. (citing Md. Cas. Co., 312 U.S. at 273).

1. Affirmative Acts by the Defendants

The Defendants assert that in order to satisfy the "affirmative act" requirement for declaratory judgment standing, there must be some act by the Defendants directed towards the Plaintiffs. As an initial matter, the Defendants have, in fact, taken specific affirmative acts toward Drs. Kazazian and Ganguly.[13] Moreover, other courts have recognized that "an overt, specific act toward the declaratory judgment plaintiff is not required to demonstrate the existence of an actual controversy." Edmunds Holding Co. v. Autobytel, Inc., 598 F. Supp. 2d 606, 610 (D. Del. 2009).

The cases cited by the Defendants

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[13] The Defendants argue that the cease-and-desist letters addressed to the University of Pennsylvania cannot be viewed as affirmative acts directed towards Dr. Ganguly. However, the letters were designed to stop the *BRCA1/2* testing being conducted by the lab jointly overseen by Drs. Kazazian and Ganguly, and Defendants seek to draw an overly formalistic distinction.

unquestionably considered the absence of "affirmative acts" directed towards the plaintiff in finding a lack of standing to bring the declaratory judgment action. None of the cases, however, establish a requirement that only acts directed towards the plaintiff could be considered for purposes of the standing analysis or even that there must exist acts specifically directed towards the plaintiffs in order to establish standing. Instead, in most of the cases, the dismissal was based on a lack of any legally cognizable acts by the defendant upon which a declaratory judgment could be established. Sec, e.g., Prasco, 537 F.3d at 1334, 1340 (observing that the plaintiff's only basis for standing was the plaintiff's allegation that its product did not infringe the defendants' patents); Indigodental GMBH & Co. KG v. Ivoclar Vivadent, Inc ., No. 08 Civ. 7657 (RJS), 2008 WL 5262694, at *2 (S.D.N.Y. Dec. 10, 2008) (concluding that "Plaintiff had done little more than become aware of Defendant's patent"); Document Sec. Sys., Inc. v. Adler Techs., Inc., No. 03-CV-6044, 2008 WL 596879, at *10 -*11 (W.D.N.Y. Feb. 29. 2008) (finding single page of deposition testimony and an unrelated patent litigation insufficient basis for standing); Broadcom Corp. v. Qualcornm Inc., No. 08cv1829 WQH (LSP), 2009 WL 684835, at *6 (S.D. Cal. Mar. 12, 2009) (citing, as the basis for its holding, plaintiff's failure "to specify any affirmative act by the defendants" that would support jurisdiction); Impax Labs., Inc v. Medicis Pharm. Corp., No. C-08-0253 MMC, 2008 WL 1767044, at *2 (N.D. Cal. Apr. 16, 2008) (finding plaintiff's filing of an Abbreviated New Drug Application coupled with defendant's public statements of intent to enforce patents insufficient to create an "actual controversy"); The Wooster Brush Co. v. Bercom Int'l, LLC, No. 5:06CV474, 2008 WL 1744782, at *4 -*5 (N.D. Ohio Apr. 11, 2008) (finding defendant had never engaged in any activity that would suggest the plaintiffs infringed its patent); Baker Hughes Oilfield Operations, Inc. v. Reedhycalog UK, Ltd., No. 2:05-CV-931, 2008 WL 345849, at *2 -*3 (D. Utah Feb. 6, 2008) (dismissing case where letters from defendant did not indicate that it thought plaintiffs were infringing its patents).[14]

A requirement that there be a specific, affirmative act directed towards the plaintiff to establish standing to seek a declaratory judgment of patent invalidity would be inconsistent with the Supreme Court's mandate that the Court examine "the facts alleged, under all the circumstances," in assessing the existence of a case or controversy. See MedImmune, 549 U.S. at 127 (quoting Md. Cas. Co., 312 U.S. at 273). As the Federal Circuit has previously stated:

> Article III jurisdiction may be met where the patentee takes a position

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[14] In Geospan Corp. v. Pictometry Int'l Corp., 598 F. Supp. 2d 968 (D. Minn. 2008), the court observed that the only instances post-MedImmune in which declaratory judgment jurisdiction had been found to exist were those in which the defendants had engaged in some form of activity against the plaintiff. Id. at 970. It did not, however, state a general rule that actions directed towards the plaintiff were required to establish subject matter jurisdiction over a declaratory judgment action, nor how such a requirement would be consistent with the "all the circumstances" test. To the extent that Geospan may be read to set forth such a requirement concerning a defendant's relevant "affirmative acts," the Court declines to adopt a similar holding.

> that puts the declaratory judgment plaintiff in the position of either pursuing arguably illegal behavior or abandoning that which he claims a right to do. We need not define the outer boundaries of declaratory judgment jurisdiction, which will depend on the application of the principle of declaratory judgment jurisdiction to the facts and circumstances of each case.

SanDisk, 480 F.3d at 1381. In light of these principles, an examination of the totality of Myriad's conduct relating to the patents-in-suit is appropriate.

The Defendants raise several challenges to the legal significance of the acts relied on by the Plaintiffs to establish standing. First, the Defendants argue that Myriad's 1998 letter to Dr. Kazazian is too old to serve as the basis for a case or controversy. The Federal Circuit cases cited by the Defendants in support of their argument, however, predate MedImmune and examined the timeliness of letters in the context of the now-defunct "apprehension of suit" test. See Sierra Applied Scis., Inc. v. Advanced Energy Indus., Inc., 363 F.3d 1361, 1374 (Fed. Cir. 2004); Cygnus Therapeutics Sys. v. ALZA Corp., 92 F.3d 1153, 1159 (Fed. Cir. 1996). Given the recent changes to the standing analysis for declaratory judgment claims, those cases no longer serve as controlling authorities. See Benitec Austl., Ltd. v. Nucleonics, Inc., 495 F.3d 1340, 1346 (Fed. Cir. 2007) (questioning holdings in prior cases applying the "reasonable apprehension of suit" test for declaratory judgment jurisdiction in light of

MedImmune). Furthermore, the Defendants cite no authority that would preclude the Court from considering the letter as part of "all the circumstances."

While the district court cases cited by the Defendants correctly applied the "all the circumstances" test in dismissing the declaratory judgment actions, they are also distinguishable from the present situation. In Avante, the affirmative act cited by the plaintiff consisted of a single, brief infringement suit lasting a few weeks. See Avante Int'l Tech., Inc. v. Hart Intercivic, Inc., No 08-832-GPM, 2009 WL 2431993, at *3 (S.D. Ill. July 31, 2009). In Edmunds Holding, the court's dismissal turned on the a finding that "[n]one of the facts adduced by [the plaintiff] established that [the defendant] believe[d] [the plaintiff] to be infringing the '517 patent." Edmunds Holding, 598 F. Supp. 2d at 610. While the Court agrees that an 11-year old letter may not, alone, be sufficient to establish declaratory judgment jurisdiction, those are not the circumstances presented here. Myriad's assertions of its patent rights consist not only of the letter to Dr. Kazazian, but a continuing course of conduct over a period of several years. In addition, Defendants' prior efforts to prevent the Plaintiffs and other similarly situated parties from engaging in *BRCA1/2* testing establish that Plaintiffs' planned activities would be considered infringing by the Defendants. The totality of the circumstances, as alleged by the Plaintiffs, cannot be said to be comparable to the circumstances presented by Avante and Edmunds.

The Defendants also dispute the relevance of prior litigation to the standing analysis. The

Defendants argue at the outset that only litigation brought against the Plaintiffs may be considered by the Court in its jurisdictional analysis; none of the cited cases, however, supports such a rule,[15] and, as discussed supra, this approach is inconsistent with the premise of the "all the circumstances" test. Further, although the lawsuits brought by Myriad against Oncormed and the University of Pennsylvania were dismissed, both serve as evidence of Myriad's willingness to assert its rights granted by the patents-in-suit against others. See Prasco, 537 F.3d at 1341 ("Prior litigious conduct is one circumstance to be considered in assessing whether the totality of the circumstances creates an actual controversy."). Finally, the suit against the University of Pennsylvania was dismissed without prejudice and therefore would not bar a new infringement action by Myriad against the University of Pennsylvania or Drs. Kazazian and Ganguly. Consequently, Myriad's prior litigations involving the patents-in-suit are fairly included in the Court's standing analysis.

The Plaintiffs cite counsel's August 11, 2009 letter to Defendants' counsel requesting a waiver of claims against intended *BRCA*-related activities and Defendants' subsequent refusal to grant such a waiver as evidence in support of the existence of subject matter jurisdiction. See Ravicher Decl. Ex. 1. However, the presence or absence of jurisdiction must be determined on the facts existing at the time the complaint under consideration was filed. GAF Bldg Materials Corp. v. Elk Corp. of Dallas, 90 F.3d 479, 483 (Fed. Cir. 1996) (citing Arrowhead, 846 F.2d at 734 n.2). Because the filing of the Complaint predated the August 11, 2009 letter, the letter does not factor into the standing analysis.

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[15] Prasco held only that the particular prior lawsuit in question did not establish the existence of a case or controversy between the parties in light of the absence of any other evidence that the defendants had taken a position adverse to the plaintiff's position. See Prasco, 537 F.3d at 1340, 1341 n.9. It did not set forth a general rule concerning the consideration of prior litigation. The court in Edmunds similarly did not prohibit consideration of prior litigation directed to third parties. See Edmunds, 598 F. Supp. 2d at 610 (distinguishing cases cited by the plaintiff in support of its assertion of the existence of case or controversy).

Taken together, Plaintiffs' allegations establish the existence of sufficient "affirmative acts" by the Defendants for purposes of declaratory judgment jurisdiction. The Defendants have asserted their right to preclude others from engaging in *BRCA1/2* genetic testing t letters, licensing offers, and litigation. The result, as alleged by the Plaintiffs and supported by affidavits, is the widespread understanding that one may engage in testing at the risk of being sued for infringement liability by Myriad. This places the Plaintiffs in precisely the situation that the Declaratory Judgment Act was designed to address: the Plaintiffs have the ability and desire to engage in *BRCA1/2* testing as well as the belief that such testing is within their rights, but cannot do so without risking infringement liability.[16]

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[16] Indeed, in light of the widespread knowledge of Myriad's *BRCA1/2* patents and the breadth of the relevant claims, a finding of patent infringement would likely be considered willful and result in treble damages. See 35 U.S.C. § 284.

In light of "all the circumstances," there exists a sufficiently "real and immediate injury or threat of future injury that is caused by the defendants" to satisfy the "affirmative act" requirement for a declaratory judgment action. Prasco, 537 F.3d at 1339; see also Adenta GmbH v. OrthoArm, Inc., 501 F.3d 1364, 1370 (Fed. Cir. 2007); Micron Tech., 518 F.3d at 899 (patentee "pursues a systematic licensing and litigation strategy").

2. Meaningful Preparations for Infringing Action

The Defendants also assert that the Plaintiffs have failed to demonstrate the existence of "meaningful preparation" to engage in infringing activity.

With respect to the researcher Plaintiffs, the Defendants argue that the Plaintiffs allege only that they are "ready, willing, and able" to infringe expressions of desire and ability are insufficient to establish "meaningful preparations" without reference to specific preparatory activities. However, the "meaningful preparation" inquiry properly focuses on whether the Plaintiffs are meaningfully prepared to engage in the infringing act such that the court's decision would serve as more than an "advisory opinion." See Cat Tech LLC, 528 F.3d at 879; SanDisk, 480 F.3d at 1381 ("[A] party need not risk a suit for infringement by engaging in the identified activity before seeking a declaration of its legal rights."). Where plaintiffs' normal course of business renders them meaningfully prepared to engage in the infringing activity at issue, the lack of some identifiable preparatory effort separate and apart from their normal activities cannot, without more, serve as the basis for finding that there has been no "meaningful preparation" for purposes of declaratory judgment jurisdiction. To hold otherwise would render those most prepared to engage in infringing activity, i.e., those for whom essentially no additional preparation is required to perform the infringing activity, the parties least likely to satisfy the standing requirements for a declaratory judgment action.

The Defendants also cite Benitec, 495 F.3d 1340, and Mega Lift Sys., LLC v. MGM Well Services, Inc., No. 6:08 CV 420, 2009 WL 1851919 (E.D. Tex. June 29, 2009), in support of their assertion that the researcher Plaintiffs' preparation is insufficient as a matter of law to establish standing. In Benitec, the Federal Circuit found the plaintiff's plans to adapt its human gene silencing technology for use in the animal husbandry and veterinary markets insufficiently immediate for standing purposes. Benitec, 495 F.3d at 1349. The court based its holding on the fact that (1) the plaintiff had merely stated that it "expect[ed]" to begin work "shortly" on adapting its existing gene silencing technology to livestock; (2) the plaintiff had provided insufficient information for the court to assess whether the plaintiff's planned activities would be infringing; and (3) the parties agreed that the plaintiff's planned activities would fall within the safe harbor provision to infringement under 35 U.S.C. § 271 (e)(1). See Benitec, 495 F. 3d at 1349. In Mega Lift, the district court relied on the fact that the plaintiff had failed to include in its complaint any "allegation about its readiness to manufacture and sell" the future product that was the subject of the declaratory judgment action. Mega Lift, 2009 WL 1851919, at *4.

The factual circumstances, as set forth in the Plaintiffs' affidavits, render Benitec and Mega Lift distinguishable on their facts and demonstrate sufficient preparation by the researcher Plaintiffs to establish standing. The Plaintiffs have demonstrated that the researcher Plaintiffs are poised to begin *BRCA1/2* testing and that the patents-in-suit present the only obstruction to doing so.[17] See, e.g., Chung Decl. ¶¶ 13, 15-18; Ledbetter Decl. ¶¶ 8-9. All are established human geneticists whose laboratories are routinely engaged in genetic testing and therefore possess the necessary equipment and expertise to immediately begin performing *BRCA1/2* genetic testing. Compl. ¶¶ 11-16; Kazazian Decl. ¶¶ 3-5, 8-11; Ganguly Decl. ¶¶ 3, 14; Chung Decl. ¶¶17-18, 21; Ostrer Decl. ¶¶ 8-10, 13; Ledbetter Decl. ¶¶ 18-19 (speaking for himself and Dr. Warren). Moreover, Drs Kazazian, Ganguly, and Ostrer had previously engaged in *BRCA1/2* testing prior to Myriad's assertion of its patent rights against them.[18] Is Kazazian Decl. ¶¶ 4-10; Ganguly

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[17] The affidavits also establish that the proposed BRCA testing would infringe the claims-in-suit and provide sufficient information to satisfy the Federal Circuit's requirement that "the existence of a case or controversy [ ] be evaluated on a claim-by-claim basis." Jervis B. Webb Co. v. Southern Sys., Inc., 742 F. 2d 1388, 1399 (Fed. Cir. 1984).

[18] Defendants argue that Drs. Kazazian and Ganguly state only that they would "consider" engaging in infringing Myriad's patents, and that such speculative intent cannot satisfy the "meaningful preparation" prong. However, the proper focus of this inquiry is whether the plaintiffs are meaningfully prepared, not whether they have made a final, conclusive decision to engage in the infringing activity. See Cat Tech LLC,

Decl. ¶¶ 3-10. Consequently, the researcher Plaintiffs are meaningfully prepared to begin "BRCA testing to advance research and/or to offer . . . an important service to the public" and "could do so within a matter of weeks." Ganguly Decl. ¶ 14; see also Ledbetter Decl. ¶ 18.[19]

Plaintiffs' affidavits similarly establish that members of the various medical organizations, represented by the organizations under the "doctrine of associational standing," are, like the researcher Plaintiffs, also meaningfully prepared and possess the desire to engage in *BRCA1/2* testing were the patents-in-suit invalidated. See, *e.g.*, Hegde Decl. I 6-12; Hubbard Decl. ¶ 3-9; Kant Decl. ¶ 4-6.

The remaining non-researcher Plaintiffs have also established the existence of sufficient "meaningful preparations" to satisfy this prong of the standing inquiry. As an initial matter, the non-researcher Plaintiffs cannot be found to have failed to satisfy the meaningful preparation requirement on the grounds that the researcher Plaintiffs have not yet chosen to engage in infringing *BRCA* testing. Potential contributory infringers, such as the non-

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528 F.3d at 879 (describing inquiry as requiring "a showing of 'meaningful preparation' for making or using that product").

[19] According to Plaintiffs' counsel, all that would be required to begin genetic testing would be to order the necessary oligonucleotides specific to the *BRCA1/2* genes, a delay of less than a month. Although Defendants raise the possibility that state certification may, in some instances, be required in order for Plaintiffs to engage in clinical *BRCA* testing, they have offered no evidence suggesting that this would constitute a delay of sufficient length to render the dispute of insufficient immediacy to warrant judicial intervention.

researcher Plaintiffs, may very well understand the precise nature of, and be prepared to take advantage of, the services of a potential infringer were the latter not prevented from offering those services by a third party's assertion of its patent rights. Here, it is alleged that the researcher Plaintiffs would offer infringing *BRCA1/2* genetic testing services of the type the non-researcher Plaintiffs would solicit or encourage others to solicit. The Defendants cite no authorities establishing that only potential direct, and not potential contributory infringers can have standing in a declaratory judgment action.[20]

The Plaintiffs have set forth sufficient factual allegations to establish that the non-researcher Plaintiffs are meaningfully prepared to engage in contributory infringement so as to render the controversy between them and the Defendants of "sufficient immediacy and reality." MedImmune, 549 U.S. at 126 (citation omitted) ; see, e.g., Matloff Decl. ¶¶ 4, 10-15; Reich Decl. ¶¶ 3, 7-11, 14-15; Brenner Decl. ¶¶ 2-3, 9; Ceriani Decl. ¶ 11; Limary Decl. ¶ 9; Girard Decl. ¶ 10; Fortune Decl. ¶ 8; Thomason Decl. ¶ 10. Indeed, for these Plaintiffs, whose infringing activity would constitute nothing more than taking advantage of alternatives to Myriad's *BRCA1/2* testing or encouraging others to do the same, it is difficult to conceive what more "meaningful preparation" would be required.[21]

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[20] Animal Legal Defense Fund, cited by Defendants, addressed the standing of a third party to challenge the findings of a PTO Examiner during examination of a patent and has no bearing on standing in the context of a declaratory judgment action. See Animal Legal Defense Fund, 932 F.2d, 920, 930 (Fed. Cir. 1991) ("A third party has no right to intervene in the prosecution of a particular patent application to prevent issuance of an allegedly invalid patent.").

The contentions of the Defendants in urging the Plaintiffs' lack of standing to bring a declaratory judgment action present a stark alternative: the deliberate violation of the patents-in-suit in order to challenge their constitutionality and validity. The risks, expense, and uncertainty of that protracted litigation process to compel the Defendants to defend the patents-in-suit are well known and recognized. Under the unique circumstances of this action and the pendency of the Plaintiffs' motion for summary judgment, the declaratory judgment procedure is preferable. It offers a far speedier and potentially less risky and protracted route to a resolution of the direct and fundamental issues. See Elecs. for Imaging, 394 F.3d at 1346.

For the foregoing reasons, the Plaintiffs possess the necessary standing to bring their claims against the Defendants.

VI. JURISDICTION EXISTS OVER THE DIRECTORS

The Defendants have moved to dismiss the Directors as defendants, pursuant to Fed. R. Civ. P. 12(b) (2), for lack of personal jurisdiction. In considering this challenge to personal jurisdiction, Federal Circuit law applies because the jurisdictional issue is "intimately involved with the substance of the patent laws." Autogenomics, Inc. v. Oxford Gene Tech. Ltd., 566 F.3d 1012, 1016 (Fed. Cir. 2009) (quoting Avocent Huntsville Corp. v. Aten Int'l Co., 552 F.3d 1324, 1328 (Fed. Cir. 2008).

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[21] Similarly, it is difficult to envision what preparatory activity would be required to infringe the claims-in-suit covering the comparison of the *BRCA1/2* gene sequence.

"In the procedural posture of a motion to dismiss, a district court must accept the uncontroverted allegations in the plaintiff's complaint as true and resolve any factual conflicts in the affidavits in the plaintiff's favor." Elecs. for Imaging, 340 F.3d at 1349 (internal citations omitted). Furthermore, because discovery has not yet been conducted, the Plaintiffs need only make a prima facie showing that the Directors are subject to personal jurisdiction. Avocent, 552 F.3d at 1329; Elecs. for Imaging, 340 F.3d at 1349.

"Determining whether personal jurisdiction exists over an out-of-state defendant involves two inquiries: whether a forum state's long-arm statute permits service of process, and whether the assertion of personal jurisdiction would violate due process." Avocent, 552 F.3d at 1329 (quoting Inamed Corp. v. Kuzmak, 249 F.3d 1356, 1359 (Fed. Cir. 2001)). "[D]ue process requires only that in order to subject a defendant to a judgment in personam, if he be not present within the territory of the forum, he have certain minimum contacts with it such that the maintenance of the suit does not offend traditional notions of fair play and substantial justice." Int'l Shoe Co. v. Washington, 326 U.S. 310, 316 (1945) (internal quotations omitted).

The Supreme Court has distinguished between "general" and "specific" forms of personal jurisdiction. General jurisdiction requires that a defendant have "continuous and systematic" contacts with the forum state. Helicopteros Nacionales de Columbia, S.A. v. Hall, 466 U.S. 408, 415-16 (1984). Minimum contacts establishing specific jurisdiction exist where "the defendant has purposefully directed his activities at residents of the forum and the litigation results from alleged injuries that arise out of or relate to those activities." Burger King Corp. v. Rudzewicz, 471 U.S. 462, 472-73 (1985) (internal quotes and citations omitted). "Once it has been decided that a defendant purposefully established minimum contacts within the forum State, these contacts may be considered in light of other factors to determine whether the assertion of personal jurisdiction would comport with 'fair play and substantial justice.'" Id. (quoting Int'l Shoe, 326 U.S. at 320). Relevant factors include "'the burden on the defendant,' 'the forum State's interest in adjudicating the dispute,' 'the plaintiff's interest in obtaining convenient and effective relief,' 'the interstate judicial system's interest in obtaining the most efficient resolution of controversies,' and the 'shared interest of the several States in furthering fundamental substantive social policies.'" Id. at 477 (quoting World-Wide Volkswagen Corp. v. Woodson, 444 U.S. 286, 292 (1980)).

In an action seeking a declaratory judgment of patent invalidity, the Federal Circuit has held that specific jurisdiction exists if "(1) the defendant purposefully directed its activities at residents of the forum, (2) the claim arises out of or relates to those activities, and (3) the assertion of personal jurisdiction is reasonable and fair." Breckenridge Pharm., Inc. v. Metabolite Labs, Inc., 444 F. 3d 1356 (Fed. Cir. 2006). "The first two factors correspond with the 'minimum contacts' prong of the

International Shoe analysis, and the third factor corresponds with the 'fair play and substantial justice' prong of the analysis." Inamed, 249 F.3d at 1360. With respect to the last prong, the burden of proof is on the defendant, which must "present a compelling case that the presence of some other considerations would render jurisdiction unreasonable." Burger King, 471 U.S. at 476-77.

The Plaintiffs assert claims against the Directors not in their individual capacities, but in their capacity as state officials, pursuant to Ex parte Young, 209 U.S. 123 (1908). The threshold question is whether, for purposes of the personal jurisdiction analysis, the contacts of the Directors as individuals or as state officials should be examined.

Under Ex parte Young, state officials are treated as state actors for all but Eleventh Amendment sovereign immunity issues, regardless of whether the conduct in question is authorized by state law. See Florida Dep't of State v. Treasure Salvos, Inc., 458 U.S. 670, 697 (1982) (suit for relief against a state officer is not barred by the Eleventh Amendment); Home Tel. & Tel. v. Los Angeles, 227 U.S. 278, 282-85 (1913) (officer sued in his official capacity treated as state actor for 14th Amendment purposes). As a result, an official capacity action is, in all but name, a suit against the governmental entity. Kentucky v. Graham, 473 U.S. 159, 165-66 (1985) ("Official capacity suits . . . 'generally represent only another way of pleading an action against an entity of which an officer is an agent.'" (quoting Monell v. N.Y. City Dep't of Social Servs., 436 U.S. 658, 690 n.55 (1978))); see also Will v. Mich. Dep't of State Police, 491 U.S. 58, 71 (1989)

("[A] suit against a state official in his or her official capacity is not a suit against the official but rather is a suit against the official's office. As such, it is no different from a suit against the State itself." (internal citations omitted)). Consistent with these principles, official capacity defendants may assert only those defenses available to the governmental entity, rather than those available to the defendant as an individual. Graham, 473 U.S. at 165-66; see also Will, 491 U.S. at 71.[22]

When confronted with the issue of specific personal jurisdiction[23] over a non-forum state official, courts routinely examine the contacts of the state officials in their capacity as representatives of the state, rather than their contacts with the forum in their individual capacity. See, e.g., Stroman Realty, Inc. v. Wercinski, 513 F.3d 476, 484 (5th Cir. 2008) (examining extent of defendant's contact with forum as a representative of the state of Arizona);[24] Grand

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[22] The treatment of state officials sued in their official capacities by the Federal Rules of Civil Procedure reflects this conception of official capacity suits. Those officials need not be identified by name; they are automatically replaced as parties by their successors; and any relief granted is automatically binding not just on the named individual but on his or her successor. See Fed. R. Civ. P. 17(d), 25(d); Hafer v. Melo, 502 U.S. 21, 25 (1991).

[23] Because specific personal jurisdiction exists over the Directors, Plaintiffs' general personal jurisdiction arguments are not addressed here

[24] Defendants cite language in Stroman which they assert refutes Plaintiffs' position. See Defs.' Mem. of Law in Opp. to Pls.' Mot. to Conduct Jurisdictional Disc. at 4 (citing Stroman, 513 F.3d at 485 ("Even if the State of Arizona itself as a sovereign state, subject to Eleventh Amendment protections derived a benefit from any 'effects' in Texas generated by the

River Enters. Six Nations, Ltd. v. Pryor, 425 F3d. 158, 166 & n.2 (2d Cir. 2005) (analyzing contacts of state attorneys general with New York as representatives of their states).

The Defendant's rely on Great Western United Corp. v. Kidwell, 577 F.2d 1256 (5th Circuit. 1978), rev'd on other grounds by Leroy v. Great Western United Corp., 443 U.S. 173 (1979), for their assertion that the jurisdictional analysis properly focuses on the contacts of the Directors as individuals with New York. In Great Western, the Court of Appeals considered whether a court in the Northern District of Texas could assert personal jurisdiction over Idaho officials enforcing an Idaho law that had "substantial consequences" in the forum. Great Western, 557 F.2d at 1265, 1267. The Defendants argue that the Fifth Circuit's opinion established that because as state cannot authorize unconstitutional action, a suit for injunctive relief against a state official in his official capacity cannot be viewed as a suit against the state. Instead, it must be viewed as a suit against the official as a private individual, and the contacts to be examined for purposes of personal jurisdiction must be the contacts of the defendant as an individual, rather than as an extension of the state.

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action of the Commissioner, the benefit does not run to those officials in their individual capacity, stripped of their sovereign immunity cloak.")). The cited language, however, in addition to being dicta, is taken from the discussion of whether a "commercial benefit" accrued to the state. It does not establish that the contacts of the official's department are not imputed to her as an official defendant for purposes of personal jurisdiction.

The discussion in Great Western cited by the Defendants, however, did not address the question of personal jurisdiction. Instead, the Fifth Circuit considered only the narrow issue of whether the Idaho official was immune from suit outside of Idaho. See id. at 1265 ("Initially McEldowney contends that his status as a state official means that even though he may be sued under Ex Parte Young . . . he may not be sued outside Idaho without his consent." (citation omitted)).[25] In contrast, when the court turned to the issue of "whether due process permits a court in Texas to exercise jurisdiction over the Idaho official who has enforced the Idaho takeover law [against a Texas corporation]," id. at 1266, the Fifth Circuit examined the actions of the defendants as representatives of the state, not as individual defendants. See, e.g., id. at 1267 (evaluating defendants' contacts with the forum by examining activities relating to the enforcement of the Idaho takeover statute). On the basis of those contacts, the court concluded that exercising personal jurisdiction over the Idaho officials pursuant to the Texas long arm statute did not violate considerations of due process. Id. at 1266.

The Defendants also rely on Pennington Seed, Inc. v. Produce Exch. No. 299, 457 F.3d 1334 (Fed. Cir. 2006). There, the Federal Circuit's opinion contained no discussion about the proper analysis for considering a state official's contacts with a forum for personal jurisdiction purposes, instead finding that there were no allegations that the university officials had the necessary contacts with the forum. Id. at 1344. The court's observation concerning the location of the officials' residences was made only in passing to note that even that fact failed to establish purposeful activity directed to the forum. Id.

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[25] To the extent the Fifth Circuit's discussion may be viewed more broadly as establishing that a state official sued in his official capacity should be treated as an individual defendant, such a holding is at odds with subsequent Supreme Court caselaw. See Hafer, 502 U.S. at 26; Will, 491 U.S. at 71; Graham, 473 U.S. at 165-66.

In light of the foregoing, the question of jurisdiction over the Directors should be resolved based upon the Directors' contacts, as representatives of the state, with New York.

Under New York C.P.L.R. § 302(a) (1), specific jurisdiction exists where a defendant "transacts any business within the state or contracts anywhere to supply goods or services in the state." A party "transacts business" when it "purposefully avails [itself] of the privilege of conducting activities within [New York], thus invoking the benefits and protections of its laws." McKee Elec. Co. v. Rauland-Borg Corp., 20 N.Y.2d 377, 382 (1967) (citation omitted). Here, the Directors have entered into an exclusive license agreement that permits Myriad to market the UURF's products and services in New York and creates continuing obligations for UURF.[26] As a result, the Directors have purposefully availed themselves of the privilege of conducting business in New York. Because the claims in this case are directly related to that license agreement and to Defendants' patent enforcement activities that have occurred in New York, the requisite "articulable nexus" between the cause of action and the business activity is present. See, e.g., Credit Lyonais Sec. (U.S.A.), Inc. v. Alcantara, 183 F.3d 151, 153 (2d Cir. 1999). Consequently, specific personal jurisdiction over the Directors exists under New York's long arm statute. See N.Y. C.P.L.R. § 302(a) (1) (2008).

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[26] See infra.

The exercise of specific personal jurisdiction over the Directors also comports with considerations of due process. The Federal Circuit has established that in the context of an action seeking a declaration of patent invalidity, due process considerations are satisfied when the defendants have (1) engaged in cease-and-desist efforts directed to parties in the forum state or attempted to license the patents at issue in the forum state;[27] and (2) entered into an exclusive license agreement with an entity that markets and sells its products and services in the forum state. See Breckenridge, 444 F.3d at 1366; see also Avocent, 552 F.3d at 1333-35; Akro Corp. v. Luker, 45 F.3d 1541, 1546 (Fed Cir. 1995); Genetic Implant Sys. v. Core-Vent Corp., 123 F.3d 1455, 1458-59 (Fed. Cir. 1997). The critical requirement for purposes of establishing due process is that the license agreement impose continuing obligations on the patentee, such as the right to enforce or defend the patents, so that the patentee maintains an ongoing relationship with the licensee operating within the forum that goes beyond the mere receipt of royalty income. See Breckenridge, 444 F.3d at 1366. The personal jurisdiction analysis of the Directors' contacts with the forum state thus turns on "the defendant's relationship with its exclusive licensee." Id. at 1365; see also Akro, 45 F.3d at 1546-47.

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[27] Although Defendants appear to assert that only cease-and-desist letters sent to a party in the forum may be relied upon to establish subject matter jurisdiction, the Federal Circuit has stated that offers to license may also serve as the requisite first point of contact with the forum. See Breckenridge, 444 F.3d at 1366 ("Thus, the crux of the due process inquiry should focus first on whether the defendant has had contacts with parties in the forum state beyond the sending of cease and desist letters or mere attempts to license the patent at issue there.").

Here, the Defendants have attempted to license the patents-in-suit to Dr. Ostrer, a resident of New York.[28] See Ostrer Decl. ¶ 7 & Ex. 2. They have also caused or participated in direct in-person cease-and-desist efforts that occurred in New York. Kazazian Decl. ¶ 6. In addition, the agreement between Myriad and UURF creates ongoing obligations on the part of the UURF beyond the mere receipt of royalty payments. As set forth in the standard licensing term sheet, UURF's policy is to retain the right to enforce licensed patents and to initiate proceedings regarding them. Ravicher Aff. Ex. 7. Myriad, of course, has a similar ability to take action enforcing the patents as demonstrated by its actions to enforce the patents-in-suit.[29] See supra. Both UURF and Myriad appear to have obligations relating to the enforcement and maintenance of the patents at issue in this lawsuit which establishes that the Directors have purposefully directed their activities at New York as a matter of law.[30] See, e.g., Avocent, 55 F.3d at 1336 ("[W]hen the patentee enters into an exclusive license or other obligation relating to the exploitation of the patent by such licensee or contracting party in the forum . . . the patentee may be said to purposefully avail itself of the forum and to engage in activity that relates to the validity and enforceability of the patent."); Breckenridge, 444 F.3d at 1366; Akro, 45 F.3d at 1546.

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[28] While the offer to license made to Dr. Ostrer was sent on Myriad Genetics' letterhead, Plaintiffs assert that Myriad and UURF acted together in asserting the rights granted by the patents-in-suit. See, e.g., Compl. IT 29, 49.

[29] Neither party contests that Myriad purposefully engages in business in New York, where it both solicits and sells a significant volume of its testing services.

In addition, the claims in this suit directly relate to the license agreement between the Defendants and their efforts to enforce the patents. See, e.g., Akro, 45 F.3d at 1548-49 ("[The patentee's] exclusive license agreement with [the plaintiff's] local competitor Pretty Products undoubtedly relates to [the plaintiff's] challenge to the validity and enforceability of the '602 patent."). Finally, the Defendants have not presented other considerations that would render it unfair or unjust for the Court to exercise jurisdiction over them.

Consequently, the Court's exercise of personal jurisdiction over the Directors satisfies the requirements of due process.

VII. THE ALLEGATIONS OF CONSTITUTIONAL VIOLATIONS ARE ADEQUATE

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[30] In addition, both the Directors and Myriad are represented jointly by counsel, further suggesting the existence of an ongoing relationship between the two entities. See Breckenridge, 44 4 F.3d at 1367.

In ruling on a motion to dismiss made pursuant to Rule 12(b) (6), the Court must accept all well-pleaded factual allegations in the complaint as true. Erickson v. Pardus, 551 U.S. 89, 94 (2007) (citing Bell Atl. Corp. v. Twombly, 550 U.S. 544, 555 (2007)). In addition, the Court must "construe[ ] the complaint liberally" and "draw[ ] all reasonable inferences in the plaintiff's favor." Chambers v. Time Warner, Inc., 282 F.3d 147, 152 (2d Cir. 2002) (citing Gregory v. Daly, 243 F.3d 687, 691 (2d Cir. 2001)). The question before the court "is not whether a plaintiff will ultimately prevail but whether the claimant is entitled to offer evidence to support the claims." Villager Pond, Inc. v. Town of Darien, 56 F.3d 375, 378 (2d Cir. 1995) (quoting Scheuer v. Rhodes, 416 U.S. 232, 235-36 (1974)). Consequently, the complaint should not be dismissed on a motion for judgment on the pleadings unless it appears beyond doubt that the plaintiff can prove no set of facts in support of its claims that would entitle it to the relief it seeks. Faconti v. Potter, 242 Fed. App'x 775, 777 (2d Cir. 2007).

The USPTO challenges the sufficiency of Plaintiffs' complaint in light of the Supreme Court's recent holding in Ashcroft v. Iqbal, 129 S.Ct. 1937 (2009). Iqbal set forth "[t]wo working principles" to guide a court's analysis of a complaint's sufficiency. Id. at 1949. "First, the tenet that a court must accept as true all of the allegations contained in a complaint is inapplicable to legal conclusions." Id. "Second, only a complaint that states a plausible claim for relief survives a motion to dismiss." Id. at 1950.

In this case, the Plaintiffs have pled sufficient factual allegations to satisfy the standard set forth in

Iqbal. The Complaint alleges the existence of a specific, written policy for the patenting of genes and the parameters of the policy. Compl. ¶ 50. The policy, contained in the Federal Register, Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001), is alleged by the Plaintiffs to be applied to a series of specific patents and patent claims. Compl. passim. The Plaintiffs describe each application of the policy in considerable detail. See, e.g., Compl. ¶¶ 55-80. Similar allegations and specificity apply to the Plaintiffs' allegations of the USPTO's practices. See, e.g., Compl. ¶¶ 53-54.

The Complaint further alleges that the information encoded in the *BRCA1/2* genetic sequences, rather than being the result of an inventive process, exists in nature. See Compl. ¶¶ 34, 46, 51, 55-60. The Complaint also alleges that the existence of certain mutations in BRCA1/2 and their correlation with an increased risk of breast and/or ovarian cancer constitutes nothing more than a naturally occurring phenomenon. See Compl. ¶¶ 61-80. Based on these factual allegations, the Plaintiffs assert that the patents-in-suit grant Myriad ownership rights over products of nature, laws of nature, natural phenomena, abstract ideas, and basic human knowledge and thought in violation of the First Amendment's protections over freedom of thought. Compl. ¶¶ 52, 54. In addition, the Plaintiffs assert that Myriad's ownership of correlations between certain *BRCA1/2* mutations and an increased risk of breast and/or ovarian cancer has inhibited further research on *BRCA1/2* as well as genes that interact with *BRCA1/2*. See, e.g., Compl. ¶¶ 96-98, 101. As a result, the patents-in-suit are alleged to violate Article I, section 8, clause 8 of the Constitution which directs Congress to "promote the Progress of Science and useful Arts . . . ." Compl. ¶¶ 52, 54.

The facts alleged in the Complaint are plausible, specific, and form a sufficient basis for Plaintiff's legal arguments. Consequently, the pleading requirements as set forth in Iqbal are satisfied.

VIII. CONCLUSION

For the reasons stated above, Defendants' motion to dismiss the Complaint is denied.

Defendants' opposition to Plaintiffs' motion for summary judgment will be due December 2, 2009. Plaintiffs' reply will be due on December 9, 2009, and argument will be heard on December 11, 2009, at ten o'clock in the forenoon in Courtroom 18C, unless good cause is shown to alter the date of the submissions.

It is so ordered.

New York, N.Y.

November 1, 2009

Robert W. Sweet

U.S.D.J.

CLAIMS

Claims 1, 2, 5, 6, 7, and 20 of patent 5,747,282 ('282)

1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID No. 2.

2. The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID No. 1.

5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.

6. An isolated DNA having at least 15 nucleotides of the DNA of claim 2.

7. An isolated DNA selected from the group consisting of:

(a) a DNA having the nucleotide sequence set forth in SEQ ID No. 1 having T at nucleotide position 4056;

(b) a DNA having the nucleotide sequence set forth in SEQ ID No. 1 having an extra C at nucleotide position 5385;

(c) a DNA having the nucleotide sequence set forth in SEQ ID No. 1 having G at nucleotide position 5443; and

(d) a DNA having the nucleotide sequence set forth in SEQ ID No. 1 having 11 base pairs at nucleotide position 189-199 deleted.

20. A method for screening potential cancer therapeutics which comprises: growing a transformed eukaryotic host cell containing an altered BRCA1 gene causing cancer in the presence of a compound suspected of being a cancer therapeutic, growing said transformed eukaryotic host cell in the absence of said compound, determining the rate of growth of said host cell in the presence of said compound and the rate of growth of said host cell in the absence of said compound and comparing the growth rate of said host cells, wherein a slower rate of growth of said host cell in the presence of said compound is indicative of a cancer therapeutic.

Claims 1, 6, and 7 of patent 5,837,492 ('492)

1. An isolated DNA molecule coding for a BRCA2 polypeptide, said DNA molecule comprising a nucleic acid sequence encoding the amino acid sequence set forth in SEQ ID No. 2.

6. An isolated DNA molecule coding for a mutated form of the BRCA2 polypeptide set forth in SEQ ID No. 2, wherein said mutated form of the BRCA2 polypeptide is associated with a susceptibility to cancer.

7. The isolated DNA molecule of claim 6, wherein the DNA molecule comprises a mutated nucleotide sequence set forth in SEQ ID No. 1.

Claim 1 of patent 5,693,473 ('473)

1. An isolated DNA comprising an altered BRCA1 DNA having at least one of the alterations set forth in Tables 12A, 14, 18, or 19 with the proviso that the alteration is not a deletion of four nucleotides corresponding to base numbers 4184-4187 in SEQ. ID No. 1.

OPPOSITION
BRIEF

Supreme Court, U.S.
FILED
OCT 31 2012
OFFICE OF THE CLERK

No. 12-398

IN THE
Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,
Petitioners,

v.

MYRIAD GENETICS, INC., ET AL.,
Respondents.

On Petition For Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

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BRIEF IN OPPOSITION

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QUESTIONS PRESENTED

1. The challenged composition claims are directed to particular isolated molecules of deoxyribonucleic acid that were identified and defined by human inventors. Did the Federal Circuit correctly apply *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), in light of *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), to conclude that these molecules, defined and isolated by human inventors, are "product[s] of human ingenuity 'having a distinctive name, character [and] use,'" particularly (i) where those isolated molecules were created by humans, do not occur in nature, and have new and significant utilities not found in nature, (ii) where the U.S. Patent and Trademark Office ("PTO") has issued similar patents since at least 1984, and issued *Utility Guidelines* in 2001 confirming that such isolated molecules are patent-eligible as human-made inventions under § 101, (iii) where investors and technology companies have placed significant reliance interests in these settled property rights over the last 30 years, (iv) where no similar challenge to the patent-eligibility of such isolated molecules has been mounted in the United States, before or since this lawsuit (and thus no conflict is alleged or could exist), and (v) where the challenged claims do not preempt or preclude the use of alternative technologies to identify a patient's cancer predisposition?

2. Did the Court of Appeals correctly apply *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), when it held that one of the challenged method claims (claim 20) was patent-eligible under § 101 because, unlike the method

claims held invalid in *Mayo*, claim 20 is based not on a law of nature but on a man-made, non-naturally-occurring transformed cell that is the product of human invention?

3. Did the Court of Appeals correctly conclude that 19 of the 20 plaintiffs recruited to join this suit lacked standing because they either had no injury traceable to Myriad, or failed to show any "controversy, between parties having adverse legal interests, of sufficient immediacy and reality" because certain plaintiffs' speculative intentions to practice the challenged patents at some unspecified time in the future did not "warrant the issuance of a declaratory judgment" under *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118 (2007)?

CORPORATE DISCLOSURE STATEMENT

No parent or publicly held company owns 10% or more of the stock of respondent Myriad Genetics, Inc. or of the University of Utah Research Foundation.

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BRIEF IN OPPOSITION

Petitioners present three unrelated questions—are Myriad's patent claims covering certain defined and isolated molecules patent-eligible compositions of matter under 35 U.S.C. § 101; was claim 20 of Myriad's U.S. Patent No. 5,747,282, covering a diagnostic method utilizing a new and never-before-known substance, properly upheld as patent-eligible; and did 19 of the 20 recruited plaintiffs lack a case or controversy with Myriad? Each was correctly answered in the affirmative by the Federal Circuit, which applied established and undisputed rules of law to the particular factual record in this case to reach these conclusions. Because these three disparate questions involve nothing more than the application of settled law to particular facts, and because this case is otherwise an exceedingly poor vehicle for this Court's review, certiorari should be denied.

BACKGROUND

A. The Longstanding Issuance Of Composition-Of-Matter Claims Drawn To Isolated DNA Molecules

The challenged composition claims are not drawn to cover "human genes" or any human being's DNA. Rather, they are limited to "isolated" BRCA molecules. Thus, to be covered by the composition claims, BRCA DNA must be "substantially separated from other cellular components which naturally accompany a native human sequence or protein," *e.g.*, it must be synthesized in a laboratory or otherwise "removed from its naturally occurring environment." C.A. App. A597.

The PTO has long recognized the human ingenuity required to create isolated DNA molecules. Applying its "specific expertise in issues of patent law," *J.E.M. AG Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 145 (2001), the PTO long ago determined that claims to "isolated" molecules of DNA reflect human-made, patent-eligible inventions. Thus, over the last 30 years it has issued thousands of patents directed to isolated DNA molecules—indeed, the challenged patents themselves began issuing 15 years ago. *See, e.g.*, Pet. App. 61a-62a; *id.* at 87a-88a (Moore, J., concurring-in-part); C.A. App. 3710. And the PTO has issued over 40,000 patents drawn to DNA-related subject matter. *See, e.g.*, Eric J. Rogers, *Can You Patent Genes? Yes and No*, 93 J. PAT. & TRADEMARK OFF. SOC'Y 19, 19, 40 (2010).

Moreover, in 2001, consistent with its longstanding practice, the PTO promulgated—after an extensive notice-and-comment process—*Utility Guidelines* formally establishing that molecules that could be derived from genetic material "can be the basis for a patent" where the particular gene (a molecule) is "isolated from its natural state and processed through purifying steps that separate the gene from other molecules naturally associated with it." 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001).

Over these 30-some years of consistent practice, and based on the PTO's *Guidelines* on patenting isolated DNA molecules, the investing and inventing communities have relied on the certainty of that patent protection to develop significant advancements in human, agricultural, and industrial products. This "outpouring of scientific creativity," reflecting "substantial investment of time and money," was "spurred by the patent system" and the decades-long understanding that isolated DNA molecules are deserving of patent rights. Pet. 88a (Moore, J., concurring-in-part).

B. Myriad's Critical Contribution To Genetic Testing And Commensurate Patent Protection

To improve individualized patient care, doctors and scientists have long devised various ways to identify a patient's hereditary predisposition to diseases. In the field of hereditary breast and ovarian cancer research, for decades preceding Myriad's specification of the BRCA genes, clinicians worked to develop methods of evaluating a patient's family history to estimate her breast cancer risk ("pedigree analysis"). While occasionally inexact, such analysis enabled a scientific estimation of risk. Still used today, pedigree analysis falls outside the patents-in-suit.

With the subsequent advent of molecular sequencing techniques, researchers sought to improve risk determination by characterizing the genes, if any, responsible for breast and ovarian cancer. In the mid-1990s respondents (collectively, "Myriad") successfully isolated the "BRCA" molecules and disclosed their creation to the world. This momentous advancement required significant skill, insight, and invention on the part of Myriad's inventors. After first devising a technique to define a particular genetic region within the genome, Myriad sought ways to assess cancer risk based on genetic mutations correlating with a predisposition to breast and ovarian cancer. C.A. App. A4802-03. Although it was believed by 1990 that there was at least one genomic region where these mutations occurred, no one had identified or defined any such region. *Id.* at A4803-04, A4771-72. Myriad did that by applying its genetic mapping technology to define the precise genetic material that its inventors called the "BRCA1 molecules," and thereafter the "BRCA2 molecules."

Once defined and specified by these human inventors, Myriad isolated those molecules from the cells in which they are found in nature and from other genomic material. *Id.* at 4804. This stage of the inventive process itself depended on an enormous amount of human judgment, including how to define the beginning and end of what came to be called the BRCA1 and BRCA2 genes, and then creating isolated DNA molecules corresponding to those particular defined genes. *Id.* at A4772-80, A4801-03, A5193-96. Myriad then used these isolated molecules to develop and launch a molecular test for targeted isolation and sequencing of a patient's BRCA DNA, which drastically improved accuracy in determining the patient's breast and ovarian cancer risk.

Myriad's inventions were universally hailed. The European Patent Office, for example, called Myriad's achievements "a major breakthrough which was not obvious to the skilled person." Board of Appeal of the European Patent Office, No. T 1213/05 at 69-70 (2007), www.epo.org/law-practice/case-law-appeals/pdf/t051213eu1.pdf ("EPO"); *see also* C.A. App. A4780 (Myriad's invention was "a scientific accomplishment that required many inventive steps, not the least of which was to contradict the scientific dogma of the time"); *accord id.* at A4769-79, A279-80, A588-89, A785-86. But these inventions did not come cheaply—they required monumental private investment. *See* Letter from Eric Y. Drogin & Robert

A. Armitage to David J. Kappos re: Genetic Diagnostic Testing (Apr. 16, 2012) 5, *available at* www.uspto.gov/aia_implementation/gene-comment-aba.pdf. Consistent with reliance on the PTO's longstanding interpretation of § 101, "[m]uch of that investment was made on a sound expectation that the risks being taken to commercialize new technology hold the promise of producing financial returns commensurate with the magnitude of the inherent risks." *Id.* With these incentives to develop the new technologies, and Myriad's public disclosures in return, the patent system worked exactly as intended.

Myriad's patent protection is commensurate with its contributions and has not inhibited others from developing additional technologies in this field. For example, gene expression profiles, inspired by Myriad's inventions but outside the scope of Myriad's patents, have been devised to test breast and ovarian cancer risk. Int'l Patent Application No. PCT/US2008/080358, Publication No. WO/2009/052417 (published Apr. 23, 2009) (Wendy S. Rubinstein, applicant). In addition, with recent advancements in sequencing techniques, random ("shotgun") sequencing and other technologies can likewise test predisposition without practicing Myriad's patents. Indeed, in 2001, seven years after Myriad's inventions, the human genome project used random sequencing to determine and publish the entire human genome sequence. In 2007, the entire genetic makeup of Dr. James Watson himself, whom petitioners invoke, Pet. 20 n.10, was characterized using whole-genome sequencing (he was found to possess a BRCA1 mutation). *See* BIO-IT WORLD, *Project Jim: Watson's Personal Genome Goes Public,* www.bio-itworld.com/newsitems/2007/may/05-31-07-watson-genome (last visited Oct. 30, 2012). Such sequencing, which does not require isolation of a BRCA-specific DNA molecule but instead randomly selects genetic material to sequence a patient's entire genetic makeup, is not covered by the challenged claims. *See* Christopher M. Holman, *Will Gene Patents Derail the Next Generation of Genetic Technologies?: A Reassessment of the Evidence Suggests Not*, 80 UMKC L. Rev. 563, 579 (2012) ("[N]o U.S. court has ever interpreted a claim to an isolated or purified DNA molecule so broadly that it would be inevitably infringed by DNA sequencing.").

Other technologies that can identify genetic mutations without infringing the challenged claims are untargeted single-molecule testing and protein-truncation testing. *See, e.g.*, *DNA Sequencing: Applications*, Oxford Nanopore Technologies, http://www.nanoporetech.com/technology/analytes-and-applications-dna-rna-proteins/dna-sequencing-applications (last visited Oct. 30, 2012); *DNA: An Introduction to Nanopore Sequencing*, Oxford Nanopore Technologies, http://www.nanoporetech.com/technology/analytes-and-applications-dna-rna-proteins/dna-an-introduction-to-nanopore-sequencing (last visited Oct. 30, 2012); Pacific Biosciences, http://pacificbiosciences.com (last visited Oct. 30, 2012); Holman, *supra*, 80 UMKC L. Rev. at 579 (Pacific Biosciences' gene-sequencing technology "relies on the observation of DNA synthesis as it occurs on an immobilized DNA polymerase, and in my view does not entail isolation of defined DNA molecules"); J.T. den Dunnen & G.J. van Ommen, *The Protein Truncation Test: A Review*, Nat'l Center for Biotechnology Info., http://www.ncbi.

nlm.nih.gov/pubmed/10425032 (last visited Oct. 30, 2012); D. Pushkarev et al., *Single-Molecule Sequencing of an Individual Human Genome*, NAT'L CENTER FOR BIOTECHNOLOGY INFO., http://www.ncbi.nlm.nih.gov/pubmed/19668243 (last visited Oct. 30, 2012).

C. District Court Proceedings

On May 12, 2009, close to 15 years after Myriad's patents issued, the American Civil Liberties Union Foundation ("ACLU") and the Public Patent Foundation ("PPF") filed a declaratory-judgment action on behalf of 20 recruited plaintiffs. Their complaint alleged, *inter alia*, that a few selected claims of Myriad's patents are patent-ineligible under § 101. Pet. App. 361a. Plaintiffs' counsel hand-selected the challenged claims, as part of a strategy of "pick[ing] one case" for a broad assault on all patents covering similar subject matter. C.A. App. A7387-88.

The district-court proceedings focused on: (1) Myriad's motion to dismiss the declaratory-judgment suit for lack of a real and immediate case or controversy; and (2) the parties' cross-motions for summary judgment on the merits.

On the jurisdictional issue, Myriad argued that seventeen plaintiffs lacked any justiciable controversy because Myriad never had any communications with them regarding the patents-in-suit. *See* Pet. App. 24a. For the remaining three (all individuals, Drs. Ostrer, Ganguly, and Kazazian), Myriad showed that any communications with them or their organizations had occurred over a decade earlier, and therefore were too stale to demonstrate a real and immediate controversy. *See id.* at 21a-23a.

Petitioners responded with declarations from various plaintiffs, including Dr. Ostrer. As the Director of NYU's Molecular Genetics Laboratory, Dr. Ostrer averred that after Myriad offered a license to NYU's laboratory in 1998 (addressed to Dr. Ostrer as the laboratory director), which NYU declined, C.A. App. A2964-74, NYU had not provided clinical sequencing for fear that Myriad would assert the challenged patents, *id.* at A2935 ¶ 7, A2934 ¶ 4. He also stated that NYU's laboratory "has all of the personnel, expertise, and facilities necessary to do various types of [BRCA1/2] sequencing," and it "could, and would . . . do full sequencing." *Id.* at A2936 ¶ 9. In their declarations, Drs. Ganguly and Kazazian averred that if the challenged claims were invalidated, they would *consider* performing BRCA1/2 testing. *Id.* at A2852 ¶ 11.

The district court sustained jurisdiction, reasoning that *MedImmune*'s "all circumstances" test does not require a patentee to have taken any action toward any specific plaintiff. Pet. App. 402a. Instead, the court stated that only "some affirmative act by the [patentee] relating to enforcement of its patent rights," regardless to whom such enforcement is directed, creates a case or controversy for any potential plaintiff. *Id.* at 399a. The court concluded that based on Myriad's activities in the late 1990s there "is the widespread understanding that one may engage in [BRCA1/2] testing at the risk of being sued for infringement liability by Myriad." *Id.* at 406a. This conclusion contradicted the evidence of widespread testing by numerous laboratories and scientists (including various named plaintiffs), without lawsuits.

The parties then cross-moved for summary judgment on the patent-eligibility of the challenged method and composition claims under § 101 as well as the First Amendment and the Patent and Copyright Clause (Article I, Section 8, Clause 8) of the U.S. Constitution.

The district court held that none of the composition claims were patent-eligible. The court identified the question presented as "whether the isolated DNA claimed by Myriad possesses 'markedly different characteristics' from a product of nature" (not, as petitioners assert here, "Are human genes patentable?"). Pet. App. 333a. It concluded that all such claims were invalid because "none of the structural and functional differences cited by Myriad" constitute a marked difference between native DNA and the claimed isolated DNA molecules. *Id.* at 336a.

Regarding method claim 20 (the only method claim at issue here), the court concluded that it was not patent-eligible because it sought "to patent a basic scientific principle." *Id.* at 355a.

D. Federal Circuit Proceedings And Petitioners' First Petition

The Federal Circuit upheld the district court's finding of declaratory-judgment jurisdiction, but only as to Dr. Ostrer. *Id.* at 153a-54a. On the merits, it concluded that the composition claims and method claim 20 were patent-eligible. *Id.* at 179a.

Petitioners did not pursue *en banc* review, instead seeking certiorari. Their questions presented were only the first and third questions presented here. Cert. Pet. at i, 132 S. Ct. 1794 (2011) (No. 11-275). Petitioners made clear that "[n]one of the method claims" was at issue. *Id.* at 7 n.2.

While their petition was pending, this Court decided *Mayo*, which involved § 101 as applied to method claims. *See* 132 S. Ct. at 1294. This Court then granted the petition in this case, vacated the Federal Circuit's judgment, and remanded for further consideration in light of *Mayo*. Pet. App. 1a.[1]

E. Proceedings On Remand

On remand, even though the petition had disclaimed a challenge to method claim 20, the Federal Circuit requested supplemental briefing on the applicability of *Mayo* to the challenged isolated DNA claims *and* claim 20. Apr. 30, 2012 C.A. Order.

First, however, Myriad filed a suggestion of mootness based on events subsequent to the Federal Circuit's now-vacated opinion: Effective August 29, 2011, Dr. Ostrer had left NYU. *See* Pls.' Answer to Defs.' Pet. for Reh'g at 2. He is instead employed by the Albert Einstein College of Medicine and Montefiore Medical Center (collectively, "Montefiore"). *Id.* There is no colorable claim of a Myriad-Montefiore controversy concerning the challenged claims. *See* Aplts.' Suggestion of Mootness at 10-13. Accordingly, Myriad suggested that the appeal was moot because whatever claim Dr. Ostrer once had to standing depended entirely on Myriad's 1998 license offer to NYU, where he no longer worked. The Federal Circuit declined Myriad's suggestion without opinion. June 11, 2012 C.A. Order. In its subsequent opinion, the court adhered to its earlier jurisdictional analysis, holding that Dr. Ostrer had standing based on Myriad's decade-old license offer to NYU because: (1) "the relevant circumstances surrounding Myriad's assertion of its patent rights have not changed"; and (2) Dr. Ostrer, through his NYU employment, "remains in the same position with respect to his ability and his desire to provide BRCA testing as in the late 1990s." Pet. App. 25a, 36a-37a. The court also adhered to its ruling that Drs. Ganguly and Kazazian had not demonstrated any controversy with Myriad, because their "some day intentions are insufficient to support an actual or imminent injury for standing," and held that the remaining plaintiffs had not shown a case or controversy either. *Id.* at 32a, 36a (internal quotations omitted).

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[1] Two months later, this Court granted, vacated, and remanded another case in light of *Mayo*. *See WildTangent, Inc. v. Ultramercial, LLC*, 132 S. Ct. 2431 (2012). *WildTangent* remains pending before the Federal Circuit.

On the merits, the court reexamined Myriad's claims to isolated DNA molecules and again held them patent-eligible, noting that the particular inquiry for composition claims remained the *Chakrabarty* test viewed, of course, in light of the fundamental principles reiterated in *Mayo*.

Judge Lourie's lead opinion for the court observed that "[w]hile *Mayo* and earlier decisions concerning method claim patentability provide valuable insights and illuminate broad, foundational principles, the Supreme Court's decisions in *Chakrabarty* and *Funk Brothers [Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948),] set out the primary framework for deciding the patent eligibility of compositions of matter, including isolated DNA molecules." Pet. App. 48a. Summarizing *Chakrabarty*'s test as whether human invention produced compositions with a "distinctive name, character and use" from what exists in nature, Judge Lourie applied that test by cataloging a variety of differences between the claimed compositions and native DNA caused by human intervention, including that isolated DNA molecules (1) are "free-standing," (2) are "synthesized" or have "chemically severed" backbones, and (3) have significantly fewer nucleotides than native DNA. *Id.* at 49a, 51a (internal quotations and brackets omitted). These differences, Judge Lourie explained, "result[ed] from human intervention to cleave or synthesize a discrete portion of a native chromosomal DNA, imparting on that isolated DNA a distinctive chemical identity as compared to native DNA." *Id.* at 52a. Thus, "we conclude that the challenged claims to isolated DNAs, whether limited to cDNAs or not, are directed to patent-eligible subject matter." *Id.* at 48a.

Concurring, Judge Moore likewise relied on "the framework of *Funk Brothers* and *Chakrabarty* in conjunction with the direction of [*Mayo*]" to analyze whether the isolated DNA claims, which she agreed are not "human genes," "have markedly different characteristics with the potential for significant utility." *Id.* at 79a. Analyzing the composition claims in three categories, she first determined that claims drawn to cDNA molecules are patent-eligible because, among other reasons, "cDNA sequences do *not* exist in nature," cDNA molecules "only contain[] the coding nucleotides," and such molecules "can be used to express a protein in a cell which does *not* normally produce it." *Id.* at 80a. Regarding claims covering isolated DNA molecules with short nucleotide sequences, Judge Moore reasoned that such claims are also patent-eligible given their different structural characteristics (*e.g.*, different chemical bonds and nucleotide sequences) as compared to native DNA, and different functional characteristics, such as the ability to be "used as primers in a diagnostic screening process" and "as the basis for probes." *Id.* at 82a. Lastly, considering claims covering isolated DNA with longer nucleotide sequences, Judge Moore determined that these claims, too, are patent-eligible, given their structural differences from native DNA. *Id.* at 85a-86a. She further explained that the patent-eligibility of these claims is confirmed by the PTO's decades-long policy of granting patents on isolated DNA molecules, and the investing and inventing communities' settled expectations of patent-eligibility for such claims. *Id.* at 87a-94a.

Even Judge Bryson, dissenting in part, looked to "the test employed by the Supreme Court in *Chakrabarty*" when addressing the composition claims. *Id.* at 110a. He agreed that one category of the challenged claims (claims drawn to cDNA molecules) are patent-eligible under that test. *Id.* at 98a. For the other composition claims, he also concurred that isolating DNA molecules results in a "material change made to those genes from their natural state." *Id.* at 102a. Judge Bryson, however, placed significantly less weight on this change than did the majority because, in his view, the change "is necessarily incidental to the extraction of the genes from the environment in which they are found." *Id.* Accordingly, like the district court, he determined, based on his own evaluation of the similarities (and not the distinctive properties engendered by isolation), that the non-cDNA composition claims were not "markedly different" from native DNA, and thus in his view not patent-eligible. *Id.* at 110a-13a.

As for claim 20, which claims "a method for screening potential cancer therapeutics via changes in cell growth rates," *id.* at 67a, the Federal Circuit applied *Mayo* and again unanimously held the claim patent-eligible. The court pointed to "transformed" cells as a key element and starting point of that claim, demonstrating its human ingenuity and distinguishing it from the claims in *Mayo*. *See id.* at 68a. Because claim 20 "is tied to specific host cells" that "are derived by altering a cell to include a foreign gene, resulting in a man-made, transformed cell with enhanced function and utility," the court rejected petitioners' argument that the claim concerned merely an abstract scientific idea about the cause of a slower growth rate, and held the claim patent-eligible. *Id.* at 68a, 70a.

F. Corrections Of Petitioners' Misstatements

Pursuant to this Court's Rule 15.2, Myriad provides the following corrections to misstatements in petitioners' recitation of fact and law.

1. The first question presented bears no relation to the uncontroverted facts of this case. Petitioners seek to present this case as asking whether "human genes" are patent-eligible. Of course, the genetic material naturally existing in every human being is not an "invention," *i.e.*, it is not the product of human ingenuity. But this case does not involve claims to such "native" human genes. The challenged composition claims are instead narrowly drawn to specific, defined DNA molecules, isolated by human scientists in laboratories, that do not naturally occur. As Judges Lourie and Moore explained, molecules of isolated BRCA1 and BRCA2 DNA are chemical "composition[s] of matter" that are just as deserving

of patent eligibility as any other human-made molecule. Indeed, numerous pharmaceutical and biotechnical inventions are claimed as specified molecules. This perhaps explains petitioners' insistence on framing their first question as "Are human genes patentable?", instead of addressing the question actually presented to and answered by the lower courts regarding the patent-eligibility of molecules defined, cultivated, and isolated by men and women through the application of human ingenuity.

2. Petitioners also contend that "[s]tandard isolation results in random DNA fragments that are identical to those that exist naturally in the body." Pet. 4. By definition, however, an "isolated" DNA molecule ***has been removed from its naturally occurring environment.*** *See, e.g.*, C.A. App. A597; *see supra* at 1-2, 4. A molecule cannot simultaneously be "removed from its naturally occurring environment" and "exist naturally in the human body"—its naturally occurring environment. As Judge Lourie explained in his lead opinion: "It is undisputed that Myriad's claimed isolated DNAs exist in a distinctive chemical form—as distinctive chemical molecules—from DNAs in the human body," because of "human intervention to cleave or synthesize a discrete portion of a native chromosomal DNA, imparting on that isolated DNA a distinctive chemical identity as compared to native DNA." Pet. App. 51a-52a.

Petitioners' belated factual claim that covalent bonds of DNA molecules may be broken in the body, Pet. 12, is irrelevant. This assertion omits critical elements of the definition of "isolated" DNA. Isolated DNA is not merely DNA that has had bonds broken;

the breaking of covalent bonds, while important, is but one part. Isolation further requires separation of the specific DNA of interest from the rest of the DNA in the body and even the rest of the fragmented DNA that may be present in a test tube outside the body. Even setting aside the human-engineered initial fragmentation breaking the covalent bonds, such *specific, precisely defined* (*i.e.*, targeted) separation does not naturally occur in the body. Thus, it is a contradiction in terms to say that "isolated" DNA exists within the body. C.A. App. A4291 ¶ 17, A4322 ¶ 133, A4324 ¶ 137, A4325 ¶ 143, A4412 ¶¶ 47-48, A4413-14 ¶¶ 51-53, A4723 ¶ 11. Even the petition elsewhere acknowledges this fact. *See* Pet. 4.

3. Contrary to petitioners' cursory and unsupported assertions, Pet. 2, 25, neither Myriad nor its patents hinder research of BRCA genes. One named plaintiff concedes that she "could sequence the BRCA1 and BRCA2 genes for purely research purposes," and has been doing so without impediment. C.A. App. A1305 ¶ 15, A1304 ¶ 11. The undisputed facts further demonstrate that 18,000 researchers have conducted studies on BRCA1/2 genes, over 8,000 relevant papers have been published on BRCA1/2 genes, and over 130 clinical trials regarding BRCA1/2 genes have commenced since Myriad publicly disclosed its inventions. *Id.* at A3643 ¶ 13, A4540-41 ¶ 41-45. Moreover, multiple laboratories provide "second opinions" regarding BRCA1/2 test results. *Id.* at A3666. In short, Myriad's patents do not hinder research. *See, e.g.*, Christopher M. Holman, *Debunking the Myth That Whole Genome Sequencing Infringes Thousands of Gene Patents*, 30 NATURE BIOTECHNOLOGY 240 (2012); John P. Walsh et al., *View from the Bench: Patents*

and Material Transfers, 309 SCIENCE 2002, 2003 (2005).

4. Petitioners allege that Myriad has "stopped other laboratories from creating and offering new and improved testing procedures" and has "the right to exclude the rest of the scientific community from examining the naturally-occurring genes of every person in the United States." Pet. 2-3. These statements are false. The challenged claims do not preempt, preclude, or prohibit others from creating and offering new and improved testing services.

To the contrary, Myriad's composition claims are limited to the precise isolated molecules it created and that are recited in the patents. These claims do not preempt or preclude other technologies that have been developed and are currently being used to study the human genome and identify genetic mutations to assess a patient's cancer predisposition—*e.g.*, gene expression profiles, whole-genome sequencing, untargeted single-molecule sequencing, and protein-truncation testing. *See supra* at 5-7. These technologies "sequence" DNA without the need for "isolation."

In fact, earlier in this case (January 2010), petitioners stated: "It is only humans' inability—currently—to sequence DNA while it is in the body that requires scientists to isolate it." Pls.' Mem. of Law at 13 (S.D.N.Y. 2010) (No. 09-4515), ECF No. 219. This falsely suggests there are only two options: sequence in the body or sequence "isolated" DNA. While DNA still cannot be sequenced in the body, DNA extracted from the body but not "isolated" can be, and has been, sequenced. For example, random sequencing and protein-truncation testing have been used for years to identify genomic variations, including BRCA mutations. More recently, multiple companies, *e.g.*, Oxford Nanopore and Pacific Biosciences, have developed single-molecule technologies that can perform untargeted sequencing of DNA, which may include BRCA genes, without infringing the challenged claims. *See supra* at 5-7.

5. Petitioners contend that the challenged composition claims "define[] the gene according to how it functions in the body—*i.e.*, that it codes for and produces a polypeptide or protein." Pet. 6. That is untrue. Each claim is a specific, defined molecule isolated from the body; none is claimed in terms of its "function." Terms such as "encoding" or "coding for" are commonly used in DNA patent claims to recite physical structure, not function—they are "structural terms" that define Myriad's human-made molecules. *See In re Deuel*, 51 F.3d 1552, 1557-58 (Fed. Cir. 1995). Petitioners' contentions to the contrary, like their insistence upon redefining the question presented as "Are human genes patentable?", reflect a misunderstanding of basic scientific principles, well-established case law, and the nature of the composition claims at issue; at a minimum, they demonstrate that the petition is grounded on disputed antecedent facts.

REASONS FOR DENYING THE WRIT

This case is unworthy of certiorari because it concerns the application of settled law to particular facts. The Federal Circuit has twice correctly applied § 101 and this Court's decisions in *Chakrabarty*, *Mayo*, and *MedImmune*. The court's decision is also consistent with the policy goal of the Patent Act, the considered judgment of the PTO, and longstanding practice. Further, the issues presented are unique and fact-bound, and in order to even reach the § 101 issues, the Court would have to take up antecedent jurisdictional questions and preempt percolation in the Federal Circuit, the appellate court statutorily vested with unifying and clarifying U.S. patent law. The Court should deny the petition.

I. THE COURT OF APPEALS CORRECTLY APPLIED THIS COURT'S PRECEDENTS TO DETERMINE THAT THE COMPOSITION CLAIMS ARE PATENT-ELIGIBLE

The Court of Appeals correctly applied § 101 and this Court's precedents to conclude that the claimed isolated molecules are human-made "compositions of matter." Section 101 is purposely "expansive" and "comprehensive," *Chakrabarty*, 447 U.S. at 308, to "ensure that 'ingenuity should receive a liberal encouragement.'" *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010) (quoting, through *Chakrabarty*, 5 WRITINGS OF THOMAS JEFFERSON 75-76 (H. Washington ed. 1871)).

When determining the patent-eligibility of composition-of-matter claims, all agree that the proper distinction is "between products of nature" and "human-made inventions." *Chakrabarty*, 447 U.S. at 313; *see* Pet. 21. At its most basic, *Chakrabarty* asks whether a purported "invention" is in fact the result of human ingenuity. *Chakrabarty*, 447 U.S. at 312-13 (something "created wholly by nature unassisted by man" is patent-ineligible, whereas something produced by man "in aid of nature [is] a patentable invention" (internal quotations omitted)). As *Chakrabarty* held, a composition created with "human ingenuity" and having a "distinctive name, character [and] use" from what exists in nature is what separates "a hitherto unknown natural phenomenon," ineligible for patent protection, from "a nonnaturally occurring manufacture or composition of matter," which is patent-eligible. *Id.* at 309-10 (internal quotation omitted).

Mayo did not disturb *Chakrabarty*, and petitioners do not argue otherwise. Rather than address the eligibility of composition claims, *Mayo* applied § 101 to the method claims in that case. Nonetheless, in the course of that analysis, *Mayo* fundamentally asked the same question that *Chakrabarty* asks: Has there been a human-made invention? *See Mayo*, 132 S. Ct. at 1293-94; 1 WILLIAM C. ROBINSON, THE LAW OF PATENTS 115 (1890) ("Every invention has its origin in man. It is his addition to the agencies already existing in nature" that creates an invention). Since all agree that *Chakrabarty* states the proper rule, petitioners' first question is not worthy of certiorari because an allegation of "misapplication of a properly stated rule of law" is rarely a legitimate basis for certiorari review. Sup. Ct. R. 10.

In any event, faithfully applying *Chakrabarty* in light of *Mayo*, the Federal Circuit correctly held that Myriad's composition claims were indeed products of human ingenuity and were thus patent-eligible. The claimed molecules squarely constitute statutory "compositions of matter"—nucleotides linked to each other by a phosphodiester backbone. *See Bilski*, 130 S. Ct. at 3226 (the term "composition of matter" is to be "understood with common usage," and citing *Chakrabarty*). Further, the record reflects that they are products of human ingenuity, not of nature. Pet.

App. 14a, 52a; C.A. App. A3493, A3709, A4290, A4317-20, A4723-24.

Petitioners themselves have repeatedly admitted that isolated DNA molecules are "compositions" of matter under § 101, and they do not argue otherwise here. Pet. App. 48a; C.A. App. A6911. Their dispute is with the Federal Circuit's application of *Chakrabarty*, based on petitioners' dismissive view that the claims' "only 'inventive concept'" "is disclosure of the law of nature." Pet. 25. Not only is this factual assertion unworthy of certiorari, but it is wholly unsupported: As Judge Lourie put it, human ingenuity, *i.e.*, invention, takes place when "human intervention has given" the claimed invention "'markedly different,' or 'distinctive,' characteristics." Pet. App. 50a (quoting *Chakrabarty*, 447 U.S. at 310); *see also Chakrabarty*, 447 U.S. at 310 (because the claims were directed to a new bacterium with markedly different characteristics from any found in nature and having the potential for significant utility, the composition "[wa]s not nature's handiwork" and the claims were patent-eligible). Judge Lourie emphasized the "inventive concept" involved in defining the structure of the claimed molecules and thus creating a new chemical entity that had never existed before. Judge Moore similarly recognized that the claimed isolated molecules "are not naturally produced without the intervention of man." Pet. App. 82a.

The Myriad inventors' numerous inventive choices—which ultimately, though far from inevitably, proved successful—yielded human-made molecules with structures and utilities different from any material existing in nature. As the European

Patent Office has observed, "[t]he positional cloning of the BRCA1 gene was very complex and involved many uncertainties," and Myriad "had to take a multitude of decisions" in defining what became known as the BRCA molecules. EPO at 12. Acknowledging that such human ingenuity produced the challenged isolated molecules, the Federal Circuit properly held the claims patent-eligible.

The Federal Circuit's holding is also consistent with the overall goal of the Patent Act to incentivize, with a limited right to exclude, those who bring new, useful inventions forward to the public. The utility of Myriad's inventions is unquestionable, and the record reflects that these never-before-isolated DNA molecules provide substantial new utilities, most notably their use as molecular tools because of their ability to target and form stable chemical structures with a BRCA DNA sequence from a patient's tissue samples. *See, e.g.*, C.A. App. A3455-57, A3468-72, A4324, A4338-43. By using these newly-created tools, a patient can now more accurately learn of her genetic predisposition to, *e.g.*, breast cancer, and in turn receive personalized medical treatment. The patent laws appropriately rewarded the women and men responsible for these inventions.

The Federal Circuit's decision is also correct in view of the PTO's longstanding practice of issuing such patents, as illustrated by its 2001 *Utility Guidelines*. These guidelines reflect the PTO's considered judgment that the definition and isolation by humans of a particular DNA molecule results from human ingenuity. In trivializing the key claim term "isolated," *e.g.*, Pet. 4, petitioners contradict the PTO's rigorous analysis underlying its *Guidelines*.

J.E.M.'s approach is on all fours with this case. There, this Court reiterated that § 101 has "broad scope and applicability," and refused to deny patent protection to sexually reproduced plants where the "PTO ha[d] assigned utility patents for plants for at least 16 years and there ha[d] been no indication from either Congress or agencies with expertise that such coverage is inconsistent with [the governing statutes]." 534 U.S. at 131, 144-45. The present case for patent eligibility is even stronger, with nearly 30 years of uninterrupted agency interpretation and practice in this area (versus 16 years in *J.E.M.*), over 40,000 DNA-related patents (versus 1,800 plant patents in *J.E.M.*), and a substantial portion of the American biotechnology sector and investing community that has relied on such settled patent protection. "'To change so substantially the rules of the game now,' after more than a century of practice, 'could very well subvert the various balances the PTO sought to strike when issuing the numerous patents which have not yet expired'" covering isolated DNA. Pet. App. 89a (Moore, J., concurring-in-part) (quoting *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002)). Moving the goalposts of patent eligibility for these patents now would also undermine the interests of the investing community: Clear and certain patent protection is critical to honor the interests of past investors, such as those who funded the research behind these inventions, but it is even more essential to economic growth that future investors—not only in biotechnology, but in all industries—know that § 101 is not subject to judicial reinterpretation just because 30 years have passed since *Chakrabarty*. *See* Pet. 16.

In short, petitioners do not dispute that *Chakrabarty* supplies the rule of decision here; they merely question its application to the facts. That is, of course, not ordinarily an appropriate reason for certiorari. And, in any event, the Federal Circuit's decision was correct. Patent-eligibility under § 101 and this Court's precedents, most significantly *Chakrabarty*, follows when human intervention brings about a new and useful composition of matter for the public good. Myriad's composition claims plainly did so here.

II. THE COURT OF APPEALS' DECISION DOES NOT CONFLICT WITH DECISIONS OF ANY OTHER APPELLATE COURT OR THIS COURT

The Federal Circuit's decision is not in conflict with any other federal appellate decision or decisions of this Court. Nor do petitioners genuinely allege a conflict. Although they contend that "the Federal Circuit departed dramatically from *Mayo*, *Chakrabarty*, *Funk Brothers*, and *American Fruit Growers*," *id.* at 22, there is no departure from precedent here, let alone a "dramatic" one.

Mayo, by its terms, concerned only the particular *method* claims before it. 132 S. Ct. at 1294. Its fundamental guidance, however, only supports the Federal Circuit's decision on the challenged composition claims. As *Mayo* explained, to be patent-eligible, claims must produce something inventive, beyond a natural law itself. *Id.* at 1293-94. Myriad's inventors applied human ingenuity to nature to create something new and useful—human-made molecules that can be used as diagnostic tools.

Petitioners themselves do not seriously contend that *Mayo* altered the relevant analysis. Indeed, they state that *Mayo* "did not settle" the patent-eligibility of the challenged composition claims. Pet. 17. That question is settled, in Myriad's favor, by this Court's longstanding precedent regarding composition claims.

Nonetheless attempting to stake their petition on *Mayo*, petitioners argue that the Federal Circuit erred in giving weight to the biotechnology community's settled expectations, in contravention of *Mayo*'s supposed "reject[ion]" of such reliance "when it invalidated certain medical patents that the PTO had approved for many years." *Id.* at 30. Not so. *Mayo* determined that the reliance interest in that case was not particularly strong, and it did so only after concluding that the method claims at issue, directed merely to laws of nature, were patent-ineligible, as precedent has long proscribed. *See* 132 S. Ct. at 1304-05. But where, as here, the precedent does not "lead[] inexorably to the conclusion that isolated DNA molecules are not patentable subject matter," Pet. App. 93a-94a (Moore, J., concurring-in-part), it is proper not to upset settled expectations. Indeed, as relevant here, *Mayo* expressly directed that courts "must hesitate before departing from established general legal rules," preferring instead that courts rely on "the role of Congress in crafting more finely tailored rules where necessary." 132 S. Ct. at 1305. Thus, far from supporting petitioners' argument, *Mayo* confirms that the Federal Circuit reached the correct result.

Petitioners also cite *Mayo* for the proposition that the § 101 inquiry "turns on whether the patent preempts use of the laws and products of nature." Pet. 22. There is no conflict here, either. The proper interpretation or application of § 101 does not "turn on" preemption. By their nature, all patent claims are preemptive. *See Mayo*, 132 S. Ct. at 1305. The vast preemptive scope of the claims in *Mayo* served only as confirmation that the Court's conclusion of patent ineligibility was correct. *See id.* at 1302 ("The presence here of the basic underlying concern that these patents tie up too much future use of laws of nature *simply reinforces* our conclusion" that the claims are patent-ineligible (emphasis added)). As the Court explained, preemption concerns arise with claims "that too broadly preempt the use of a natural law." *Id.* at 1294.

Here, by contrast, Myriad's inventions do not preempt, much less "too broadly preempt," natural law. Numerous alternatives are available for determining a patient's predisposition to breast and ovarian cancer without using isolated BRCA molecules. *See supra* at 5-7. Moreover, the patent protection Myriad received covers its human-made contributions and no more. *See Mayo*, 132 S. Ct. at 1303 (the concern is "how much future innovation is foreclosed relative to the contribution of the inventor"). No law of nature is tied up by patenting a new, specific, defined, and useful molecule, as Myriad has done here. The existence of multiple other technologies currently used to determine cancer predisposition is dispositive evidence of the lack of any improper preemption. *See supra* at 5-7.

As for the other three precedents petitioners cite, there is likewise no conflict. They merely show that a legal rule applied to different facts may yield different results. In *Chakrabarty*, this Court upheld the patent-eligibility of a bacterium because the claim was "not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity 'having a distinctive name, character and use.'" 447 U.S. at 309-10 (quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887)). Here too, the particular claimed molecules are "a product of human ingenuity" that, because of their definition and isolation by human inventors, have been given new characteristics from the "native" gene embedded in the genome, and substantial new utilities as diagnostic tools. Pet. App. 59a ("isolating genes to provide useful diagnostic tools and medicines is surely what the patent laws are intended to encourage and protect").

The Federal Circuit's decision is also in perfect harmony with *Funk Brothers* and *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1 (1931), cases that anticipated *Chakrabarty's* test but, on their particular facts, reached different results. In *Funk Brothers*, the combination of preexisting, commercially available strains of bacteria "d[id] not disclose invention or discovery" (under the pre-1952 Patent Act, which equated "invention" with "nonobviousness" under current § 103). 333 U.S. at 132. In *American Fruit Growers*, the small amount of borax added to the rind of a fresh orange did not constitute a "manufacture" because there was no "change in the name, appearance, or general character of the fruit." 283 U.S. at 11-12. Unlike those claims, the isolated DNA molecules here take on different properties and utilities upon their isolation from native DNA, and those differences are the direct consequence of human intervention. Pet.

App. 51a; *id.* at 82a, 89a-90a (Moore, J., concurring-in-part).

In arguing that the results in *Funk Brothers* and *American Fruit Growers* should govern, petitioners mischaracterize the claims here as merely a "blueprint" for "coding for" the genetic material in the body; under this view, petitioners say, the patents claim only a natural function. Pet. 24. This is factually incorrect and mischaracterizes the claim language. The patents do not claim the compositions with reference to their functions; and the "coding for" language is a structural, not a functional, limitation in the claims. *See In re Deuel*, 51 F.3d at 1557-58. The composition claims are limited to claims for a specific, precisely defined composition with a specific, non-naturally occurring structure—a particular, human-defined, isolated DNA molecule. *See supra* at 14-16, 18. As the Federal Circuit ruled, the claims are directed to a specific and new chemical entity that does not exist in nature and that has uses unrelated to how the "code" operates in the body. Pet. App. 44a-46a, 50a-51a (unlike natural DNA "exist[ing] in the body as one of forty-six large, contiguous DNA molecules," the claims are drawn to "a free-standing portion"); *accord id.* at 81a-82a (the claims "are truncations" that "are not naturally produced without the intervention of man").

Meanwhile, since the PTO first began issuing patents drawn to isolated DNA molecules over 30 years ago, "claims similar to the ones at issue in this case have been the focal point of important litigation." *Id.* at 88a (Moore, J., concurring-in-part) (citing *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200 (Fed. Cir. 1991)). Yet no appellate court has ruled them ineligible. In *Amgen*, although § 101 ineligibility was apparently pled as an affirmative defense, *see* 927 F.2d at 1204, it was not the subject of any appellate decision. Indeed, no appellate court has ruled any composition claim ineligible since § 101's current formulation was included in the 1952 Patent Act. Without any conflict, this Court's review is unwarranted.

III. THE COURT OF APPEALS CORRECTLY DETERMINED THAT CLAIM 20 IS PATENT-ELIGIBLE

Petitioners' challenge to the patent-eligibility of method claim 20 does not warrant review. Indeed, petitioners had already abandoned their challenge to this claim when they failed to seek its review in their prior petition. This vehicular problem stands as a threshold obstacle to petitioners' challenge here. Further, the patent-eligibility of claim 20 is a fact-bound question that need not detain this Court. *See* Sup. Ct. R. 10.

In any event, the Federal Circuit correctly applied *Mayo* to hold that claim 20, which claims a method for screening cancer therapeutics, is patent-eligible. Under *Mayo*, a method claim is patent-eligible if it "do[es] significantly more" than describe natural laws. 132 S. Ct. at 1297. The *Mayo* claims "simply t[old] doctors to gather data from which they may draw an inference in light of the correlations" and provided no "practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself." *Id.* at 1297-98. Accordingly, the claims had not done significantly more than describe a natural law and thus were patent-ineligible. *Id.*

Claim 20, by contrast, "does significantly more" than simply describe natural laws. Indeed, the claim starts not with a "natural law" (as in *Mayo*), but with a new and useful product of human ingenuity—"a transformed eukaryotic host cell containing an altered BRCA1 gene causing cancer"—and applies additional steps to that transformed cell so that a new, useful, and inventive method of determining the efficacy of a cancer therapeutic was made available to the public. Pet. App. 427a. Each transformed cell, central to the claim, is a non-naturally-occurring, human-made creation that is plainly more than what exists in nature. Thus, the claim "includes more than the abstract mental step of looking at two numbers and 'comparing' two host cells' growth rates," *id.* at 68a, and "recites patent-eligible subject matter under § 101," *id.* at 70a.

Petitioners argue that the Federal Circuit misapplied *Mayo* by putting too much emphasis on the transformed cell, Pet. 31-32, and they proclaim—without record support—that "transformed cells containing altered DNA are conventional products widely available for purchase." *Id.* at 32. Nothing in the record even suggests that such "transformed cells" were available at the time of the invention, much less now. Moreover, petitioners fail to explain why these considerations, even were they true, overcome the fact that each transformed cell is non-naturally-occurring. Lastly, contrary to petitioners' overstatement that the method claim "[p]revent[s] any researcher from engaging in this science to find a cancer treatment," *id.*, the claim "is tied to specific host cells *transformed* with specific genes and grown in the presence or absence of a specific type of therapeutic," Pet. App. 70a. Properly characterized, claim 20 is patent-eligible, and the Federal Circuit's correct decision presents no basis for this Court's review.

IV. JURISDICTIONAL PROBLEMS OVERWHELM THE PETITION

Petitioners' third question presented seeks to overturn the Federal Circuit's jurisdictional ruling against 19 of the 20 plaintiff-petitioners. In raising this threshold question last, petitioners seek to elide the jurisdictional deficiency inherent in their petition. Because the Federal Circuit properly rejected the asserted standing of those 19 plaintiffs, the justiciability of this case rests entirely on one individual, Dr. Ostrer. His standing would have to be addressed before reviewing the § 101 questions, because the "case-or-controversy requirement subsists through all stages of federal judicial proceedings, trial and appellate." *Lewis v. Continental Bank Corp.*, 494 U.S. 472, 477-78 (1990).

According to the Federal Circuit, Dr. Ostrer had standing based on his affiliation with an NYU laboratory that had once received and declined a license offer from Myriad to practice the patents-at-issue. Although Dr. Ostrer, not NYU, is the named plaintiff, NYU is plainly the real party in interest. Otherwise, whoever is the personal addressee of a letter like Myriad's letter to NYU would have personal standing, regardless whether the organizational affiliation remained, contrary to fundamental principles underlying standing to bring a lawsuit. Pet. App. 34a (noting that Dr. Ostrer's standing stemmed from Myriad's 1998 license offer to NYU, which would "require[] NYU to make a payment to Myriad" for certain BRCA1/2 testing performed by that laboratory).

But Dr. Ostrer no longer works at NYU, and his new employer, Montefiore, has never had any controversy with Myriad. Indeed, Myriad and Montefiore have never communicated about the patents-in-suit. *See* Aplts.' Suggestion of Mootness, Decl. of R. Marsh. Whether or not the 1998 Myriad-NYU correspondence created a controversy between Dr. Ostrer and Myriad at the time suit was filed in 2009, and Myriad maintains that none existed then, any such controversy certainly evaporated by 2011; it did not follow him to Montefiore.

On these facts, although the Federal Circuit denied Myriad's suggestion of mootness, a substantial question remains regarding Dr. Ostrer's continued standing. This Court would have to consider this issue to assure itself of Article III jurisdiction before reaching any of the § 101 issues.

Although petitioners seek to overcome this obstacle by arguing for the standing of the other plaintiffs, petitioners themselves apparently do not have confidence in those arguments, raising those threshold jurisdictional arguments only as their final question presented. Indeed, petitioners' arguments allege no decisional conflict; they merely, and incorrectly, state that the Federal Circuit adopted a "new and inflexible rule" regarding declaratory-judgment jurisdiction. Pet. i. That court, however, plainly analyzed standing according to this Court's precedent, looking properly to the existence of a bilateral controversy, and not the subjective feelings or perceived inhibitions of the plaintiffs alone. Pet. App. 28a-42a. Thus, even setting aside Dr. Ostrer's lack of standing, petitioners' final question presented, asking whether the Federal Circuit correctly applied settled law to the other plaintiffs, is not worthy of certiorari.

V. THIS CASE IS A POOR VEHICLE FOR REVIEW

Additional vehicular problems render this case a poor candidate for the Court's review.

First, this case represents an abstract challenge to Myriad's patents. Petitioners alone selected the particular claims to challenge, leaving unchallenged several claims that they concede will continue to impede BRCA sequencing and other conduct in which they seek to engage: "Myriad has obtained patents on DNA as probes. Claim 6 of '473 is one example and not challenged here." Pls.' C.A. Br. at 16; *see also* C.A. App. A432-23, A6973 ¶ 40, A7021. Accordingly, there exist significant issues of redressability, yet another antecedent jurisdictional problem with the petition. *See, e.g., Lujan v. Defenders of Wildlife*, 504 U.S. 555, 561 (1992).

Second, Myriad was unable to assert counterclaims of infringement because no plaintiff was actually conducting any BRCA-related testing services; accordingly, this Court's review would be inhibited because the exact scope of the challenged claims has not been defined. The district court performed only limited claim construction, and without infringement assertions the courts had no reason to determine the precise scope of the claims' exclusionary rights. Yet petitioners themselves argue that this Court will have to address questions of claim construction to properly analyze patent-eligibility. *See* Pet. 28 (asserting that Judge Lourie's conclusion "contradicts both the patent claim language . . . and this Court's repeated admonition that patents should be evaluated according to the actual claim language"). Moreover, much of petitioners' effort to obtain this Court's review is premised on their unsubstantiated speculation that Myriad's claims will inhibit those "who want to undertake testing and research involving the patented genes in order to improve diagnosis and treatment for patients" and will "exclude the rest of the scientific community from examining the naturally-occurring genes of every person in the United States." *Id.* at 2-3, 20, 27 n.12. Such assertions have never been tested in any adversary proceeding. And had they been tested, they would have been exposed as false, for several non-infringing technologies for determining a patient's cancer predisposition are currently available. *See supra* at 5-7. Likewise, with no review of the form of testing petitioners might utilize, to determine whether such testing would infringe, there has been no analysis of what the claims do *not* cover, *e.g.*, whole-genome sequencing. These obstacles are additional antecedent problems, neither mentioned nor fairly included within the questions presented, that make this case a poor vehicle.

Third, as to the patent-eligibility of the challenged composition claims, there is not a single opinion for the panel. Petitioners seek to make this a reason for review. Pet. 16-17. But, had there been a true need to reconcile divergent judicial viewpoints, it would have been appropriate for petitioners to first seek *en banc* review from that court. *See, e.g.*, *Bilski*, 130 S. Ct. at 3224-25, 3231 (noting the Federal Circuit's statutory task of unifying patent law); *Festo*, 535 U.S. at 729-30; *Warner-Jenkinson Co. v. Hilton Davis*

Chem. Co., 520 U.S. 17, 23-24 (1997). For whatever reasons, they did not. Meanwhile, in a case that petitioners contend demonstrates those judges' "divergent views" on patent-eligibility under § 101, Pet. 18, the Federal Circuit has granted *en banc* review to consider the patent-eligibility of certain method claims in light of *Mayo*. *See CLS Bank Int'l v. Alice Corp. Pty. Ltd.*, Order, No. 2011-1301 (Fed. Cir. Oct. 9, 2012). It is thus apparent that, if the patent-eligibility of composition claims like these did present an important and recurring issue, the Federal Circuit stands ready to consider such a question *en banc*.[2]

Fourth, the relevance of patenting isolated human DNA is ever diminishing in light of the publication of the entire human genome in 2001 (several years after the 1994 and 1995 filing dates of the patents-in-suit), thus presenting arguable bars to patentability under other provisions of the Patent Act (such as obviousness under § 103) for any claims to isolated human DNA molecules sought after that date. Further, such patents issued before the 2001 publication of the entire human genome will soon expire—Myriad's patents-in-suit all expire by 2015. Thus, the unique facts of this case, presenting issues unlikely to recur, make it an inappropriate candidate for certiorari.

Fifth and finally, despite over 30 years of isolated DNA patents, this case is the first and still only appellate decision to address the patent-eligibility of such compositions. In nonetheless challenging these claims, it is clear that petitioners seek, via judicial ruling, a change in the settled understanding of § 101 that allows patents on isolated genetic molecules. *See* Pet. 19-20. Such efforts, particularly with the deeply settled reliance interests of the technology and investing communities at stake, should be addressed to Congress, not the courts. *See Mayo*, 132 S. Ct. at 1305. As Judge Moore recounted, Congress is "[f]ar from oblivious to the patenting of genes [citing several bills regarding gene patents]" and "is obviously aware of the issues presented in this case"; "'any recalibration of the standard of patentability remains in its hands.'" Pet. App. 92a-93a (quoting *Microsoft Corp. v. i4i Ltd.*, 131 S. Ct. 2238, 2252 (2011); brackets omitted).

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[2] Also pending before a Federal Circuit panel is another § 101 case. *See WildTangent*, 132 S. Ct. 2431; n.1, *supra*.

Moreover, any consideration of the settled expectations that isolated molecules are patent-eligible should take into account the consequences of a legal rule that would apply far beyond the realm of human DNA. Many biotechnology companies' intellectual-property endeavors, and the investors on which those companies rely, depend on patents covering isolated DNA corresponding to non-human genes. Advancements in these other areas allow, *e.g.*, beverages to be clarified, food starches broken down, paper recycled, clothes cleaned and softened, and agricultural waste reduced to fuel. Altering the expectations that these useful developments will be patent-protected is the role of policymaking, not adjudication. *See Chakrabarty*, 447 U.S. at 317.

For any or all of these reasons, this case lacks the "important" and "compelling" attributes required for this Court's review.

CONCLUSION

The petition should be denied.

Respectfully submitted,

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October 31, 2012

REPLY
BRIEF

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,

Petitioners,

—v.—

MYRIAD GENETICS, INC., ET AL.,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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INTRODUCTION

This Court has taken a balanced and nuanced view in distinguishing unpatentable compositions and methods that cover laws or products of nature from genuine, patentable inventions. *See, e.g., Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012); *Diamond v. Chakrabarty*, 447 U.S. 303 (1980); *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948). The Federal Circuit, by contrast, has strained to minimize the product/law of nature doctrine in order to find virtually everything patentable. *See, e.g., Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 628 F.3d 1347 (Fed. Cir. 2010), *rev'd sub nom. Mayo*, 132 S. Ct. 1289; App. at 8a-96a; Pet. at 18 (listing cases). This case presents the simple question of whether removing a human gene from the body and cell makes it patentable.

Respondents Myriad Genetics *et al.* (Myriad) argue that because the Circuit paid lip service to *Chakrabarty* and *Mayo*, its opinion is consistent with this Court's approach and the law is settled. Br. in Opp'n at 19-20 ("BIO"). But even a cursory reading of the majority opinions reveals the degree to which they diverged. Myriad also argues that its patents are valid because they are beneficial, not completely preemptive, and justified by industry reliance on PTO practice. BIO at 2-7. These arguments do not comport with *Mayo* and are, in any event, contradicted by the facts. *See infra* Section I.

Myriad attempts to avoid the undisputed facts about the stunning nature and scope of its patent claims by ignoring the claim language. *E.g.*, BIO at 1-4; *see infra* Section II. Its final argument that this case presents a poor vehicle for review is also fundamentally flawed. BIO at 31-36. As the first opportunity in thirty years to clarify the Court's product of nature doctrine, this case is the appropriate vehicle for such a review. BIO at 31-36; *see infra* Section III.

I. THE FEDERAL CIRCUIT CREATED NEW LEGAL RULES THAT DIVERGED FROM THIS COURT'S PRECEDENTS.

Despite Myriad's claim that the law applied by the Circuit is settled, it is clear that the Circuit created new legal standards in upholding these patents, while simultaneously rejecting those articulated in this Court's Section 101 precedents.

Myriad distorts the Circuit's opinion beyond recognition. For example, Myriad describes Judge Lourie's opinion as faithfully applying the "distinctive name, character, and use" standard. BIO at 11-12. Of course, this Court has applied other standards in analyzing patent eligibility, including whether the invention has "markedly different characteristics from any found in nature." *Chakrabarty*, 447 U.S. at 310. And contrary to Myriad's contention, Judge Lourie never referred to a different "name" for the genes, which are called the same thing whether in or out of the body. He explicitly rejected the idea that any different function or use of the gene when "isolated" was even relevant to the Section 101 question. App. at 52a, 55a. And when discussing structure (or character), he referred to only one factor, breaking of a covalent bond, *id.* at 53a-55a, which Myriad remarkably tries to bolster by suggesting isolated DNA is "free-standing" and shorter. BIO at 12-14; *but see* App. at 102a-13a.

Myriad describes Judge Moore as holding that claims to longer segments of DNA are "patent-eligible, given their structural differences from native DNA." BIO at 13. But she quite clearly says the opposite, upholding the patents based on industry reliance in spite of her view that "isolated" full-length genes may not be markedly different from genes in the body. App. at 85a-86a.

Both the Federal Circuit and Myriad pay only brief lip service to *Mayo* and prior opinions, gutting them of content to justify patenting a law/product of nature. The majority did not see *Mayo* as relevant to composition claims, App. at 58a, even though these claims preempt use of laws of nature as well as products of nature. For example, claim 6 of patent '492, claims *any* "isolated DNA molecule coding for a mutated form of the BRCA2 polypeptide... associated with a susceptibility to cancer." App. at 427a. The claim broadly preempts using any person's DNA to investigate the correlation between BRCA2 mutations and one or more cancers, without specifying or disclosing either the clinically significant mutations or the cancers for which patients may be susceptible. This and the other isolated DNA claims challenged here preempt scientific inquiry, disproportionately tying up both products and laws of nature. *See Mayo*, 132 S. Ct. at 1301.

Myriad asserted its patents to stop every other laboratory in the U.S. from offering clinical sequencing of these genes and providing patients with their own genetic information. App. at 37a. Myriad exercised its rights to threaten laboratories that were using different testing methods from

Myriad's, such as the University of Pennsylvania laboratory run by petitioners Arupa Ganguly and Haig Kazazian and that was sued by Myriad. App. at 34a. Because clinical genetic testing provided to patients in the U.S. relies on isolated DNA, these patents are of huge concern to the medical and scientific communities and patients, both those with hereditary conditions or disease predisposition and those who might benefit from treatments tailored to their genome. *See, e.g.*, Br. of Amici Curiae Am. Med. Ass'n *et al.*, Oct. 30, 2012; Br. for Canavan Foundation *et al.* as Amici Curiae, Oct. 30, 2012; Amici Curiae Br. for Academics in Law, Medicine, Health Policy and Clinical Genetics, Oct. 30, 2012 ("Academic *Amici* Brief"); App. at 4a-7a.

Myriad attempts to dispute how its patents monopolize the BRCA genes by pointing to other potential testing methods it contends would not violate its patents. Its flawed argument inadvertently establishes the preemptive effect of its patents. First, some of the tests mentioned do not sequence DNA at all; instead, they measure other biological phenomena, such as gene expression and proteins. They do not involve the natural phenomena at issue here – a person's genetic sequence – and their existence is irrelevant to whether the product and law of nature at issue – the DNA – is preempted. And because these tests measure different biological phenomena, they are not at all appropriate alternatives to DNA sequencing. That Myriad would resort to distracting the Court with references to these methods illustrates the deeply problematic and preemptive effect of its patents. Second, other methods cited by Myriad would violate the patent claims as defined by the

Circuit. For example, whole genome sequencing involves the breaking of DNA's covalent bonds, which Judge Lourie found to be key to defining isolated DNA. Myriad for the first time suggests otherwise, but the plain claim language belies its suggestion. *See* App. at 116a-17a. In the guise of explaining the scope of its claims, Myriad actually is rejecting the interpretation of the claims set out by the district court and Circuit. But for a patentee to assert that it would not enforce its rights against certain activities simply does not diminish their preemptive effect. The patents give Myriad the power to determine what testing can or cannot be done relating to patented genes and chill scientific work and innovation that could be pursued by the medical community.

Allowing the Circuit's opinion to stand would undo core holdings of *Funk Brothers*, recently cited by the Court in *Mayo*, 132 S. Ct. at 1293-94, and introduce a new legal standard for Section 101 eligibility – permitting a patent on a composition whenever it is removed from its natural environment and has some increased utility. Myriad emphasizes that the Circuit found that isolated DNA is patentable because it is DNA removed from its natural environment. BIO at 1. Yet, under *Funk Brothers*, removal of something from its natural environment is not sufficient to render it patentable. The patented strains of bacteria in *Funk Brothers* were "isolated," removed from their natural environment, and aggregated so as to more efficiently fix nitrogen without inhibiting each other. 333 U.S. at 129-30. They still could not be patented. *Id.* at 132. Moreover, the concurring opinion in this case held that claims covering short DNA segments were acceptable under *Funk Bros.* because they had new utility as primers and probes. App. at 82a-83a. The claims here are not limited to uses of isolated DNA as primers or probes; but even if they were, increased utility does not by itself cross the Section 101 threshold. The court of appeals in *Funk Brothers* "thought that Bond did much more than discover a law of nature, since he made an new and different composition of non-inhibitive strains which contributed utility and economy to the manufacture and distribution of commercial inoculants." 333 U.S. at 130-31. But the Court found that despite this, Section 101 was not satisfied: "[T]here is no invention here unless the discovery that certain strains of the several species of these bacteria are non-inhibitive and may thus be safely mixed is invention. But we cannot so hold without allowing a patent to issue on one of the ancient secrets of nature now disclosed." *Id.* at 132. Nevertheless, the Circuit concurrence would uphold patents whenever the composition has increased utility – even utilities undescribed in the patent claims at issue, App. at 83a-85a – while the majority found utility irrelevant, App. at 55a. Both undermined central holdings of *Funk Brothers* and *Chakrabarty*. Finally, Myriad goes so far to suggest, as it argued in the proceedings below, that *Funk Brothers* is not relevant to Section 101 but instead to Section 103, BIO at 27, despite this Court's repeated reliance on *Funk Brothers* in its Section 101 decisions. *Mayo*, 132 S. Ct. at 1293-94; *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010), *Chakrabarty*, 447 U.S. at 309; *Parker v. Flook*, 437 U.S. 584, 591 (1978); *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972).

The Circuit's decision distorts the Section 101 analysis in other crucial ways that will impact future cases. The Circuit ignored this Court's clear instruction in *Mayo* that the Section 101 question should be decided irrespective of whether patentees have substantial reliance interests. *Mayo,* 132 S.Ct. at 1304-05. For the concurrence in this case, these interests were the decisive factor in upholding patents on full-length genes, App. at 86a, and Myriad similarly reiterates the importance of the industry's interests. This reasoning cannot be reconciled with this Court's precedents, such as *Mayo*, *Bilski*, *Chakrabarty*, *Flook*, *Benson*, *Funk Brothers*, and *American Fruit Growers v. Brogdex Co.*, 283 U.S. 1 (1931), where patents were found invalid based on the legal principles laid out by this Court without regard to reliance interests or PTO practice. In *Mayo*, this Court admonished against providing enhanced protection for specific fields. *Mayo*, 132 S.Ct. at 1305; Pet. at 23-24. Yet in this case, the majority held as a matter of law that it was improper to consider the biology of genes since the only relevant question was one of chemistry. App. at 55a. *See also* Academic *Amici* Brief at 18-22 (explaining how the Circuit committed a fundamental error in construing the claims based on chemistry, rather than biology).

II. THE PATENT CLAIMS REACH PRODUCTS/LAWS OF NATURE AND NOT INVENTIONS.

Petitioners have already explained the nature of the claims and the reasons why they reach products/laws of nature. *E.g.*, Pet. at 6-7.

Respondents' only real response is to misrepresent the claim language.

Myriad's first argument is to emphasize that they have only patented "isolated" DNA, not DNA in the body. *E.g.*, BIO at 1. But, Myriad concedes that "isolation" means nothing more than "substantially separated from other cellular components" and "removed from its naturally occurring environment." *Id.* In other words, they patented the human genes simply pulled out of the body. Myriad argues it altered the DNA from the composition it has in the body. *E.g.*, BIO at 15. Petitioners already addressed this. *E.g.*, Pet. at 24-25, 28-29; *see also* App. at 102a-05a, 333a-44a. If the genes outside the body were so different from that inside the body, Myriad's testing of the "isolated" genes would be diagnostically useless. Pet. at 5. Three of the four judges who have written in this case determined there were no structural changes that alone qualify isolated DNA as an invention. App. at 81a-82a, 86a, 102a, 333a. Moreover, while removing the DNA from its natural environment allows the gene to be examined by scientists, the properties of DNA that the majority of the Circuit and Myriad point to are the product of the routine process of isolation, not of any "invention" by Myriad. *See* App. at 51a, 82a-85a (describing qualities of the patented DNA, that would describe any gene that is isolated). Had Myriad been the first to isolate a gene, it could have patented the method. But it cannot now claim that any characteristics of DNA incidental to isolation justify its patents. Isolated genes simply cannot be said to have "markedly different characteristics from any found in nature."

Myriad's second argument is that they identified the region of the overall human chromosome that correlated with an increased risk of breast and ovarian cancer. BIO at 3-4. Of course, many other scientists laid the foundation for these discoveries, including Dr. Mary-Claire King, who identified the locus of the BRCA1 gene. App. at 99a, 273a-77a. Even giving due credit to Myriad for its contribution, it is hard to imagine a more perfect definition of "we identified a law of nature." Myriad also makes repeated self-serving arguments, largely unsupported by the record, about the difficulty of identifying the relevant gene and making it available for testing. *E.g.*, BIO at 4. Yet, patents are not a reward for effort. The difficulty and complexity of uncovering $E=mc^2$ cannot be overemphasized, but that law of nature is clearly not patentable.

Myriad argues repeatedly that it was simply patenting a "molecule." *E.g.*, BIO at 14. Again, that is irrelevant. If nature made the molecule, as it did, it is not patentable. Myriad did not invent the length, composition, or function of the BRCA1 or BRCA2 molecules; human biology determined these qualities of the two genes. App. at 106a-07a, 339a, 342a-44a. Moreover, Myriad did not patent "a" molecule but literally hundreds of millions of molecules, many of which Myriad has never described and never seen and all of which make up naturally-occurring BRCA1 and BRCA2 genes. Pet. at 6-7. Thus, Myriad claims *any* DNA that codes for a particular protein or *any* part of that protein. It claims the full-length BRCA genes and *any* segments of them as short as 15 nucleotides. It claims not only the wild-type or normal genes, but *any* mutations of the genes, known and unknown. Thus, it claims the molecules that are the BRCA1 and BRCA2 genes of every one of the more than 300 million people in the United States and almost innumerable small segments. *E.g.*, App. at 105a-06a (one claim alone includes an "almost incalculably large number of new molecules"); Pet. at 7.

In other words, Myriad's claims are not inventions; they represent products and laws of nature and the fundamentally erroneous conclusion of the Circuit to the contrary merits review.

III. THIS CASE IS THE PROPER VEHICLE TO REVIEW THESE ISSUES.

Myriad proposes various weak arguments that this case is not an appropriate vehicle for review. The opposite is true. First, Myriad argues that the petitioners will not be able to test for harmful mutations in the BRCA genes if these claims are declared invalid because other claims would also preclude examination of the genes. BIO at 33. Myriad made this argument to the Circuit, which properly and unanimously rejected it. App. at 39a-40a.

Second, the record is sufficient for review free of factual disagreement. Myriad itself moved for summary judgment based on this record, which included dozens of declarations. App. at 237a. In addition, a large number of *amicus* briefs, virtually all from organizations with expertise, have acknowledged there is no fundamental dispute on the facts.

Third, Myriad hints that this Court should await a further *en banc* Federal Circuit argument on the law relating to method claims. BIO at 34-35.

But, this case is about composition claims as well as method claims and there is no vehicle of which petitioners are aware that will resolve the lower court confusion on this doctrine except through the granting of the petition.

Patent claims like the ones at issue will continue to be relevant for many years to come. Even setting aside the broader issue of the product of nature doctrine, the USPTO continues to issue new patents on human genes. *See, e.g.*, U.S. Patent 7,928,212 (filed June 16, 2010). Moreover, Myriad has control over patents on isolated BRCA DNA that will not expire for more than another decade, allowing it to continue to exclude the medical and scientific community from undertaking important clinical work relating to these genes. *See, e.g.*, U.S. Patent No. 7,250,497 (filed June 9, 2003) (titled "Large Deletions in Human BRCA1 Gene and Use Thereof" and expiring June 9, 2023).

Finally, Myriad once again trots out its argument that none of the plaintiffs has standing. BIO at 31-33. The Circuit unanimously rejected this argument on three occasions. App. at 25a, n.6. In addition, Myriad made this same argument to this Court in opposing the prior petition, yet the Court granted the petition. App. at 1a. That Myriad continues to advance the argument highlights the narrow standing rules applied by the Federal Circuit, which are inconsistent with this Court's holding in *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118 (2007), and which led the Federal Circuit to improperly deny standing to the other plaintiffs in this case. *See* Pet. at 32-35. If anything, therefore, Myriad's standing argument simply reinforces the need for this Court to grant Question 3 presented by the Petition.

CONCLUSION

For all these reasons, petitioners respectfully ask that the petition be granted.

Respectfully submitted,

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Dated: November 9, 2012

AMICUS
CURIAE
BRIEF

Supreme Court, U.S.
FILED
OCT 30 2012
OFFICE OF THE CLERK
SUPREME COURT, U.S.

No. 12-398

In The Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,
Petitioners,

v.

MYRIAD GENETICS, INC., ET AL.,
Respondents.

ON PETITION FOR WRIT OF CERTIORARI
TO THE UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

BRIEF OF AMICUS CURIAE AARP IN SUPPORT OF PETITIONERS

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INTEREST OF AMICUS CURIAE[1]

AARP is a nonpartisan, nonprofit organization dedicated to addressing the needs and interests of people age fifty and older. AARP seeks through education, advocacy, and service to enhance the quality of life for all by promoting independence, dignity, and purpose. In its efforts to promote independence, AARP works to foster the health and economic security of individuals as they age by attempting to ensure the availability of quality and economical health coverage. AARP has a long history of advocating for access to affordable health care and for controlling costs without compromising quality.

Access to affordable health care is particularly important to the older population, which has higher rates of chronic and serious health conditions. Genetic tests are capable of diagnosing a variety of diseases, assessing the risk of future disease, and enabling treatment to be tailored to individual genetic variations. Patents such as those present in this case significantly elevate the cost of genetic testing, prohibit diagnosis and treatment based on second medical opinions. In light of the significance of the issue presented in this case, AARP respectfully submits this amicus curiae brief urging the Court to grant the petition for writ of certiorari.

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[1] In accordance with Supreme Court Rule 37.6, AARP states that: (1) no counsel to a party authored this brief, in whole or in part; and (2) no person or entity, other than AARP, its members and its counsel have made a monetary contribution to the preparation or submission of this brief. All parties have received at least ten days notice of AARP's intent to file a brief. Written consent of the parties has been obtained and will be filed with the Clerk of the Court pursuant to Supreme Court Rule 37.2.

SUMMARY OF THE ARGUMENT

The Federal Circuit erred in holding that isolated DNA was patentable. DNA molecules and human genetic sequences are natural phenomena that when discovered are not the kind of "discovery" that Section 101 protects. If the Federal Circuit's decision is permitted to stand, there will be grave public health implications. Specifically, patients will be prevented from seeking a second opinion from another laboratory before making potentially life-altering decisions to undergo prophylactic mastectomies or receive other medical treatment.

Additionally, the monopoly created by the patents in this case has allowed the patent holder to charge fees that are unaffordable to many people effectively denying them life-saving medical treatment. While the patent system involves a delicate balance between the need for innovators to recoup research and development expenditures and protecting the public, the ultimate object of the patent laws has always been to benefit, not harm the public.

ARGUMENT

I. The Court Should Grant Certiorari Because The Federal Circuit Refused To Even Consider The Public Health Impact That Results From Denying High-Risk Patients A Second Medical Opinion.

The Court has long recognized that "the rights and welfare of the community must be fairly dealt with and effectually guarded" in the patent system *Kendall v. Winsor*, 62 U.S. 322, 329 (1859). More recently, the Court held that courts must consider the public impact when considering injunctive relief in patent cases. *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 391. The Federal Circuit erred when it essentially held that whether or not women would be denied a second medical opinion was irrelevant. Specifically, the Federal Circuit dismissed the serious health consequences of its decision by erroneously holding that this case "...is not about whether individuals suspected of having an increased risk of developing breast cancer are entitled to a second opinion". *Ass'n For Molecular Pathology v. United States PTO*, 689 F.3d 1303, 1324 (Fed.Cir. 2012). Unfortunately, that is precisely what this case is about and the Federal Circuit committed reversible error by refusing to even consider the public health consequences of its decision.

The patent system involves a delicate balance between the need for innovators to recoup research and development expenditures and the protection of the public. Public interest in the patent system must take into account public health. The ultimate object of the patent laws has always been to benefit, not harm the public. *See Kendall v. Winsor, supra.* "A patent by its very nature is affected with a public interest. As recognized by the Constitution, it is a special privilege designed to serve the public purpose of promoting the 'Progress of Science and useful Arts.'" *Precision Instrument Mfg. Co. v. Auto. Maint. Mach. Co.*, 324 U.S. 806, 815-16 (1945). *See also* U.S. Const. art. I, § 8.

Patents should not be used to deprive the public of the best and safest medical treatment. *See e.g., Hybritech, Inc. v. Abbott Labs.*, 849 F.2d 1446, 1458 (Fed. Cir. 1988)(noting that while there exists a public interest in protecting rights secured by valid patents, the public's needs must also be considered)[2]; *Vitamin Technologists, Inc. v. Wis. Alumni Research Found.*, 146 F.2d 941 (9th Cir. 1945) (holding that patents that limited low income persons' access to a vitamin that combats rickets were invalid). It is a principle of general application that courts can consider the public interest when granting equitable relief and these principles apply equally to patent cases. *See, eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 391 (2006).

Gene patents, such as Myriad's, significantly harm the public interest by maintaining an environment in which patients are unable to obtain a second opinion when other laboratories are precluded from conducting genetic tests due to patents. Additionally, the monopoly created by the patent has allowed the patent holder to charge excessive fees and effectively deny many people life-saving medical treatment.

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[2] The preliminary injunction standards were revised on other grounds in *Winter v. Natural Resources Defense Council, Inc.*, 555 U.S. 7 (2008). *See also eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388 (2006).

A. Gene Patents Impede The Ability Of Patients To Obtain The Best Medical Care.

Information gained from genetic tests can have a profound impact on medical decision-making. For many, the results from genetic testing can inform crucial life-altering decisions such as whether to undergo prophylactic mastectomy, or take a particular drug. Kathy L. Hudson et al., *Oversight of US Genetic Testing Laboratories*, 24 Nature Biotechnology 1083, 1083 (2006). Research released this year indicates that BRCA2 mutation carriers may be at a heightened risk of cardiac failure if certain chemotherapy treatments are used. Krishna K. Singh et al., *BRCA2 Deficiency Exaggerates Doxorubicin-Induced Cardiomyocyte Apoptosis and Cardiac Failure*, J. Biological Chemistry, 287 J. of Biological Chemistry 6604 (2012). If treating physicians are not aware of a patient's BRCA2 deficiency, they might prescribe chemotherapy that increases the risk of cardiac failure. *Id.* In order to receive proper treatment it is crucial that both patients and the medical professionals treating them have full access to genetic tests including confirmatory tests at different laboratories.

Referencing the present case, the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) noted in an April 2010 report that "an exclusive rights holder's clearance of the market denies all patients of the ability to access a confirmatory genetic test from a different laboratory." U.S. Dep't of Health & Human Servs., *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests: Report of the Secretary's Advisory Committee on Genetics, Health, and Society* 44 (2010), [hereinafter SACGHS 2010 Report], http://oba.od.nih.gov/oba/sacghs/reports/SACGHS_patents_report_2010.pdf. The Committee stated that the ability to obtain a confirmatory test from a second laboratory is "the laboratory equivalent to the time-honored practice of obtaining a second opinion from a clinician." *Id.* In the absence of a second opinion, laboratory errors and inaccurate test results can result in "misdiagnosis, inappropriate and/or delayed treatment, anxiety and in rare cases, even death." Hudson, *supra*, at 1089. Independent confirmatory testing is especially important, given the "implications for major medical decisions, such as whether to have a mastectomy or surgical removal of the ovaries." SACGHS 2010 Report, *supra*, at 44.

A 2008 study of decision-making in 338 women who underwent BRCA testing determined that risk-averse women who are high-risk and test positive for a BRCA1/2 mutation are likely to opt for more invasive and irreversible preventative procedures, such as a prophylactic mastectomy (*i.e.*, preemptive breast removal surgery). Sandra van Dijk et al., *Decision Making Regarding Prophylactic Mastectomy: Stability of Preferences and the Impact of Anticipated Feelings of Regret*, 26 J. Clinical Oncology 2358, 2360 (2008). The study determined that fear of a future cancer diagnosis is often a factor in the decision-making process regarding treatment options and that decisions regarding treatment options cause very high levels of anxiety, particularly for women who fear that choosing anything short of the most aggressive treatment option may leave their children motherless. *Id.* at 2362.

Under the Federal Circuit's ruling, exclusive rights holders such as Myriad deny patients access to a second opinion by preventing other laboratories from offering confirmatory testing. A study of more than 130 genetics laboratories found that 25 percent had no choice but to stop performing or developing a clinical genetic test due to the exclusionary effects of a gene patent. Mildred K. Cho et al., *Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services*, 5 J. Molecular Diagnostics 3, 5 (2003). While Myriad has allowed others to perform basic research on BRCA1 and BRCA2 "participation in research studies is not an adequate substitute for providing the most effective and thorough clinical genetic testing." Tom Walsh et al., *Spectrum of Mutations in BRCA1, BRCA2, CHEK2, and TP53 in Families at High Risk of Breast Cancer*, 295 J. Am. Med. Ass'n 1379, 1386 (2006). Only reports from Clinical Laboratory Improvement certified laboratories can be reported to patients or used in clinical care and it may take months or even years before patients receive their results from research laboratories, if at all. *See e.g.*, Ebony B. Bookman et al., *Reporting Genetic Results in Research Studies: Summary and Recommendations of an NHLBI Working Group*, 140 Am. J. Med. Genetics 1033, 1034 (2006); Misha Angrist et al., *Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Long QT Syndrome*, 12 Genetics Med. S111, S127 (2010).

With genetic tests, the need for access to a second opinion is especially critical because studies have shown that Myriad's BRCA tests do not detect all known mutations. Tom Walsh et al., *supra* at 1380. A study at the University of Pennsylvania further found that 8 percent of non-Ashkenazi Jewish test subjects carried a BRCA mutation not detectable by Myriad's standard test. Maurizia Dalla Palma et al., *The Relative Contribution of Point Mutations and Genomic Rearrangements in* BRCA1 *and* BRCA2 *in High-Risk Breast Cancer Families*, 68 Cancer Research 7006, 7011 (2008).

Not only do Myriad's tests underrepresent cancer risks, at least one study suggests that the mutation prediction models used by Myriad to counsel patients regarding whether to even obtain BRCA1/2 testing can be grossly inaccurate among portions of the population. Allison W. Kurian et al., *Performance of BRCA1/2 Mutation Prediction Models in Asian Americans*, 26 J. Clinical Oncology 4752, 4756 (2008). The study found that the models used by Myriad significantly underestimate the prevalence of BRCA1/2 mutations among Asian American women. *See id.* at 4754-55.

The treatment options available to a patient with a high risk of developing breast or ovarian cancer are invasive, expensive, and often carry a heavy emotional and psychological cost. Multiple genetic tests have reached different conclusions than Myriad's, and the science governing genetic testing continues to advance. Eileen M. Kane, *Patent-Mediated Standards in Genetic Testing*, 2008 Utah L. Rev. 835, 849 (2008). Since the implications of incorrect genetic test results are grave, it is imperative that patients not be prevented from seeking a second opinion.

II. Patents On Genetic Sequences Interfere With The Practice Of Medicine And Harm Patients.

Gene patents force millions of Americans with limited health care coverage and personal resources to forgo potentially life-saving testing. They allow sole providers of a genetic test to exclude other laboratories from serving patients. Access to genetic testing is particularly difficult for large segments of the Latin American/Hispanic population who are disproportionately poor and uninsured or underinsured. Lloyd Runser, Cabrina Eagan, & Danielle Olds, *The Uninsured and Underinsured*, http://www.case.edu/med/epidbio/mphp439/Safety_Nets.htm (last visited Oct. 26, 2012).[3] Recent data released by Myriad indicates that Hispanic patients who need BRCA testing need the full range and more costly BART analysis. *See* Myriad Genetic Labs., Inc., *BRCA1 and BRCA2 Prevalence Tables for Mutations Detected by Sequencing, the 5-Site Rearrangement Panel (LRP) and the BRACAnalyis Large Rearrangement Test (BART) in High Risk Patients*, http://www.myriad.com/lib/brac/BART-table-faq.pdf (last visited Oct. 26, 2012).[4]

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[3] *See also* Office of the Assistant Sec'y for Planning & Evaluation, U.S. Dep't of Health & Human Servs., *Overview of the Uninsured in the U.S.: An analysis of the 2005 Current PopulationSurvey* (2005), http://aspe.hhs.gov/health/reports/05/uninsured-cps/index.htm#race.

Gaining access to genetic testing is also particularly challenging for Medicare and Medicaid patients because gene patents allow exclusive rights holders to place limits on the forms of insurance that they will accept. Clinicians have reported access problems "when an exclusive rights holder does not accept a particular insurance, but enforces its patents to narrow or clear the market." SACGHS 2010 Report, *supra*, at 43. Specifically, two Emory University genetic counselors commented that "there are also labs [that are exclusive licensees or patent holders] that choose not to contract with Medicaid or Medicare at all." *Id.* SACGHS concluded in its April 2010 report that "patient access problems . . . are caused not by any behavior by health insurers, but by an exclusive rights holder's decisions" and that "[i]f other laboratories could offer [these genetic tests] . . . patients would have a greater chance of obtaining access . . . ." SACGHS 2010 Report, *supra*, at 44-45.

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[4] *See also* Yale Cancer Genetic Counseling, *An Open Letter to Myriad Genetics* (July 22, 2011), http://yalecancergeneticcounseling.blogspot.com/2011/07/open-letter-to- myriad-genetics.html.

In the present case, while Myriad does have a financial assistance program, neither Medicaid nor Medicare recipients are eligible to apply. Myriad Genetic Labs., Inc., *Billing & Payment Options*, https://www.myriadpro.com/billing-insurance/reimbursement-payment-options (last visited Oct. 26, 2012) ("Due to regulatory limitations, patients who are recipients of government funded programs [i.e. Medicaid, Medicare] or those that have any third-party insurance are not eligible to apply for MFAP.").

The lack of competition also keeps "costs of tests comparatively high." Cancer Council Austl., Clinical Oncological Soc'y of Austl., *Senate Inquiry into Gene Patents* 6 (2009), http://bit.ly/Rd5fGd (noting that costs can remain high despite advances in technology or efficiency elsewhere in the system).[5] There are an estimated 226,870 new cases of invasive breast cancer in women and about 39,570 deaths from breast cancer each year. *See* Am. Cancer Soc'y, *Breast Cancer Facts and Figures 2012* 9 (2011). Those at risk for cancer often have no choice but to forgo potentially life-saving health care treatment because they lack health care coverage or the resources to pay for genetic testing out-of-pocket. "[T]he failure to obtain health care in a timely fashion is associated with negative outcomes, including more costly care, delays in diagnosis or treatment and poorer health outcomes, and premature death." Stefanie Mollborn et al., *Delayed Care and Unmet Needs Among Health Care System Users: When Does Fiduciary Trust in a Physician Matter?*, 40 Health Services Research 1898, 1899 (2005) (citations omitted).

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[5] *See also* Joshua Sarnoff et al., *Submission of American Patent and Health Law Professors on Australian Senate Community Affairs Committee Inquiry Into Gene Patents*, March 18, 2009 ("Gene patents increase the cost of the diagnosis and treatment of genetic diseases. For up to twenty years, a gene patent holder controls *any* use of 'its' gene. The patent holder can charge whatever it wants for any test analyzing the patented gene—even if that test uses a technology that was not invented by the patent holder.").

A. Gene Patents Limit Access To Genetic Testing For Patients Covered by Medicare.

Medicare is the largest health insurance provider in the United States, serving approximately 49 million older and disabled Americans.[6] *See* U.S. Dep't of Health & Human Servs., *Coverage And Reimbursement of Genetic Tests and Services: Report of the Secretary's Advisory Committee on Genetics, Health, and Society* 4 (2006), [hereinafter Coverage and Reimbursement], http://oba.od.nih.gov/oba/sacghs/reports/CR_report.pdf; Kaiser Family Found., *Medicare Spending and Financing Fact Sheet* 1 (Sept. 2011), http://www.kff.org/medicare/upload/7305-06.pdf. In 2010, the median annual income of Medicare beneficiaries was $21,183. Kaiser Family Found., *Projecting Income and Assets: What Might the Future Hold for the Next Generation of Medicare Beneficiaries?* 1 (June 2011), http://www.kff.org/medicare/upload/8172.pdf. Additionally, one in four beneficiaries spend 30 percent or more of their income on health expenses. Kaiser Family Found.,

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[6] "Older" under Medicare is age 65 or older.

Medicare Spending and Financing Fact Sheet 2 (Sept. 2011), http://www.kff.org/medicare/upload/7305-06.pdf.

Gene patents preclude a substantial portion of the Medicare population from accessing potentially life-saving genetic tests. Medicare policy limits coverage of BRCA tests to Medicare recipients with a personal history of cancer who meet additional criteria despite U.S. Preventive Services Task Force recommendations to test women with a family history of cancer who have not yet contracted cancer. *See e.g*, Grace Wang et al., *Eligibility Criteria in Private and Public Coverage Policies for BRCA Genetic Testing and Genetic Counseling*, 13 Genetics Med. 1045 (2011). Currently Medicare's coverage of the actual BRCA test is more limited than private insurance companies. Wang, et al, *supra*. Requiring Medicare patients to actually contract cancer before covering the BRCA1/2 test eliminates the primary benefit of predictive testing. Further, individuals who do not meet the criteria for the test are forced to either pay the exorbitant expense of the test out-of-pocket or forgo testing altogether.

B. Gene Patents Limit Access To Genetic Testing For Patients Covered by Medicaid.

Medicaid beneficiaries often suffer from similar problems of access and affordability, due to gene patents, as those experienced by Medicare beneficiaries. "Overall, Medicaid beneficiaries are much poorer and in markedly worse health than low-income people with private insurance." Kaiser Family Found., *MEDICAID: A Primer, Key Information on Our Nation's Health Coverage for Low-Income People* 7 (2010), *available at* http://www.kff.org/Medicaid/upload/7334-04.pdf. Coverage for genetic testing varies from State to State, often depending on the States' respective revenues and political climates. House Budget Comm. on the Budget, *The Path to Prosperity: Restoring America's Promise* 25 (2011), *available at* http://budget.house.gov/UploadedFiles/PathToProsperityFY2012.pdf (indicating the Medicaid system is "broken"); Coverage and Reimbursement, *supra*, at 32. Some Medicaid programs do not consider BRCA testing to be a covered service. Wang et al., *supra*, at 1048. Individual State fiscal policies make "it extremely difficult for the Medicaid population to secure access to new [genetic] tests and services over the long term." Coverage and Reimbursement, *supra*, at 32. *See also* Ryan Crowley, American Coll. of Physicians, *Medicaid and Health Care Reform* 4-5, http://www.acponline.org/advocacy/where_we_stand/policy/reform_medicaid.pdf (highlighting the financial constraints limiting state Medicaid coverage). These differences in State Medicaid coverage "may constitute a significant source of disparate access to genetic tests and services, especially since Medicaid beneficiaries may not have other health insurance coverage or be able to pay for care out-of-pocket." Coverage and Reimbursement, *supra*, at 32.

With this uncertain health care framework in place for Medicaid beneficiaries, the access problems created by exclusive gene patents are acute for these low-income individuals. Even Medicaid recipients who live in states that cover BRCA testing have difficulty getting testing because Myriad refuses to accept their Medicaid. Lisbeth Ceriani, one of the plaintiffs, spoke candidly in the District Court about how Myriad Genetics holds Medicaid recipients' fate and future in its administrative hands because it could choose to accept or reject her Medicaid insurance.

> I am currently insured through MassHealth, a Medicaid insurance program for low-income people in Massachusetts. Although my health insurance covers genetic testing done through contracted laboratories, Myriad refuses to contract with MassHealth. I was told that Myriad refuses to accept the $1599 reimbursement rate that MassHealth offers for the test. Myriad is the only laboratory in the U.S. that provides full BRCA gene sequencing, so it is impossible for MassHealth to "contract" with another laboratory to cover this test for its insured.

Ceriani Decl., filed in U.S. Dist. Ct. for the S.D of N.Y., at 2, ECF No. 53.

Patents granting exclusive rights to perform genetic tests exacerbate problems with coverage and reimbursement in the health care system. *See e.g.*, Misha Angrist et al., *supra,* at S127 (2010). Patents additionally create unique issues of access for the Medicaid and Medicare recipients who need genetic tests. These problems are not limited to Myriad's BRCA1/2 test, but actually arise with other genetic tests offered by patent rights holders. SACGHS 2010 Report, *supra*, at 42-44. Patients are seeking access now, but gene patents are creating difficulties that health care reforms cannot resolve. Therefore, it is important that gene patents, such as those owned by Myriad, be rejected.

III. The Federal Circuit Erred In Holding That Isolated DNA Is Patent Eligible Under 35 U.S.C. § 101.

DNA molecules and human genes are natural phenomena that when discovered are not the kind of "discovery" that Section 101 protects. "Laws of nature, natural phenomena, and abstract ideas' are not patentable." *Mayo Collaborative Services v. Prometheus, Inc.*, 566 U.S. __, 132 S. Ct. 1289, 1293 (2012) (quoting *Diamond v. Diehr*, 450 U.S. 175, 185). The relevant distinction for purposes of Section 101 is "...between products of nature...and human-made inventions". *Diamond v. Chakrabarty*, 447 U.S. 303, 313 (1980) "The laws of nature, physical phenomena, and abstract ideas have been held not patentable." Id. at 309; *Diamond v. Diehr*, 450 U.S. 175, 185 (1981). "Mere recognition" of an already existing phenomenon is not patentable. *Parker v. Flook*, 437 U.S. 584, 593 n. 15 (1978) ("Patentable subject matter must be new [novel]; not merely heretofore unknown."). Further, insignificant physical steps such as isolating and removing DNA cannot transform unpatentable natural phenomena into a patentable invention. In *Wood-Paper Patent*, 90 U.S.

566 (1874), the Court found that merely removing pulp from straw, wood, or other natural sources did not make it a patentable new composition of matter: "A process to obtain it [an extract] from a subject from which it has never been taken may be the creature of invention, but the thing itself when obtained cannot be called a new manufacture." *Wood-Paper Patent*, 90 U.S. at 593-94. Similarly, isolating a gene or DNA from the human body does not then make the isolated DNA itself patentable. DNA molecules, regardless of whether they are isolated and cleaved, are natural phenomena and are not patent eligible under 35 U.S.C. § 101.

CONCLUSION

For the foregoing reasons, AARP respectfully urges the Court to grant the petition for *writ of certiorari*.

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October 30, 2012

AMICUS
CURIAE
BRIEF

RECORDS AND BRIEFS

OCT 26 2012

No. 12-398

IN THE

Supreme Court of the United States

ASSOCIATION FOR MOLECULAR
PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondent.

ON PETITION FOR A WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

AMICI CURIAE BRIEF FOR ACADEMICS IN LAW, MEDICINE, HEALTH POLICY AND CLINICAL GENETICS IN SUPPORT OF PETITIONERS

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INTEREST OF THE *AMICI CURIAE*[1]

Amici Curiae are academics in law, medicine, health policy and clinical genetics. Collectively, they have advised the governments of the United States, Canada, South Africa, the United Kingdom and Australia, as well as international governmental organizations including the Organisation for Economic Co-operation and Development (OECD), the European Union and the World Health Organization on human gene patents and life science innovation. Specifically, they chaired a task force of the Secretary's Advisory Committee on Genetics, Health and Society on human gene patents, testified before Congress on genetic testing, drafted guidelines for the OECD on the licensing of genetic inventions, prepared a report for the OECD on IP management in the life sciences, prepared Opinions for the European Commission on intellectual property issues in life sciences, drafted reports for the U.S. Congress, prepared multiple case studies on gene patenting in the United States and prepared submissions to Australian law reform inquiries into gene patenting.

Dr. E. Richard Gold, LLB, S.J.D., is a James McGill Professor in the Faculty of Law at McGill University. He has authored an extensive case study of Myriad Genetics and its patenting policies and was the Expert Consultant who drafted the OECD Guidelines on the Licensing of Genetic Inventions. He practiced law in the areas of intellectual property licensing and financing of small to medium technology companies and has provided judicial education in the United States, Canada and France on questions of intellectual property, property and the life sciences. He also heads intellectual property and technology transfer research within the Value Addition through Genomics and GE3LS (VALGEN), a publicly financed research project on agriculture and crop biotechnology.

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[1] Counsels of record have each received timely notice of the intent to file this brief under Supreme Court Rule 37. The petitioners have filed a letter of blanket consent to filing *amicus* briefs. The respondents granted consent to *amici* on October 17, 2012 via electronic mail. The *amici* submitting this brief and their counsel hereby represent that no party to this case nor their counsel authored this brief in whole or in part, and that no person other than *amici*, using research funds provided by VALGEN, paid for or made a monetary contribution toward the preparation and submission of this brief.

Dr. James P. Evans, M.D., Ph.D., is Bryson Distinguished Professor of Genetics and Medicine in the School of Medicine at the University of North Carolina. He is a board certified Medical Geneticist and Internist with extensive clinical and research expertise in the area of genetics and genetic testing, including the analysis of the BRCA1/2 genes in both the research and clinical setting. He chaired the Task Force that laid the groundwork for Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Testing: Report of the Secretary's Advisory Committee on Genetics, Health, and Society (U.S. Department of Health and Human Services, April 2010). He is also the editor-in-chief of Genetics in Medicine, the journal of the American College of Medical Genetics.

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Dr. Julian Kinderlerer is Professor of Intellectual Property Law at the University of Cape Town, South Africa, Professor of Biotechnology and Society at the Technical University, Delft, The Netherlands and a Former Director of the Sheffield Institute of Biotechnological Law and Ethics in the United Kingdom. He heads the Research Unit on Intellectual Property Law and Policy at the University of Cape Town. He is also

President of the European Group on Ethics in Science and New Technologies (EGE) that advises the European Commission, Council and Parliament on Ethical issues. He has written extensively on patent issues in relation to the life sciences for the European Commission and has served on several UK advisory bodies in relation to the use of genetically modified organisms.

SUMMARY OF ARGUMENT

Certiorari is required to redress the Federal Circuit's disregard for this Court's decisions, most notably that of *Mayo v. Prometheus*, 132 S.Ct. 1289 (2012). This Court's intervention is further necessitated by the uncertainty that the Federal Circuit introduced over patent eligibility not only in the field of human clinical genetics but in the life sciences generally. Finally, this case offers the Court with the opportunity to further develop its holding in *Mayo* concerning the independent and important function of the 35 U.S.C. § 101 in determining patentable subject matter.

By refusing to modify its vacated decision in any significant manner following this Court's remand in the present case, the Federal Circuit disregarded the Court's admonition that patent law not inhibit "more future invention than the underlying discovery could reasonably justify." (*Mayo* at 1301). This Court in *Mayo* provided a strong rationale for § 101 having an important role independent of §§ 102, 103, and 112, a rationale largely ignored by the Federal Circuit's majority and concurring opinions.

Beyond its legal errors, the Federal Circuit introduced confusion into the determination of patent eligibility under

§ 101 in at least three respects: (1) it introduced a bright-line test of covalent bond-breaking for patent eligibility of naturally occurring biological molecules; (2) it set out two conflicting tests of the meaning of "markedly different" under this Court's holding in *Chakrabarty*; and (3) it assessed the claims at issue from the point of view of a chemist when the patent applicant had specifically set out the field of art as being genetics.

Because the effects of this decision will be felt in many areas of the life sciences in which natural molecules are involved, it is critical that this Court provide guidance in line with its decisions in *Mayo* and *Bilski* on the application of § 101 to DNA molecules, in particular, and compositions of matter in general.

ARGUMENT

Certiorari is required in this case to correct the introduction by the Federal Circuit of a bright-line, yet scientifically incoherent, test for patentability under 35 U.S.C. § 101 that contradicts the principles laid down by this Court in *Mayo v. Prometheus*, 132 S.Ct. 1289 (2012). The Federal Circuit's test not only ignores the fundamental balance sought to be achieved through patent law, but introduces such new uncertainty into the determination of which natural molecules can be patented as to pose a serious risk to investments not only in clinical genetics, but in the life sciences more generally. This appeal provides the Court with an opportunity to assess, for the first time, claims covering naturally occurring molecules that have not been altered in such a manner as to change their biological function or utility.

I. THE DECISION OF THE FEDERAL CIRCUIT CONFLICTS WITH DECISIONS OF THIS COURT WITH RESPECT TO THE SCOPE OF § 101

This Court, in *Mayo*, provided a clear understanding of the independent role played by the exception to patentable subject matter implicit in § 101 relating to laws of nature, natural phenomena, and abstract ideas. This understanding has four elements.

A. The Four Elements of the *Mayo* Test for Patent Eligibility

First, § 101 implicitly contains *one* overarching exception with three sub-components—laws of nature, natural phenomena and abstract ideas—and not three distinct exceptions. ("The Court has long held that this provision contains *an important* implicit exception. '[L]aws of nature, natural phenomena, and abstract ideas' are not patentable." (*Mayo* at 1293, citations omitted, emphasis added.) The three sub-components are simply convenient ways to address different aspects of one central, principled exception rather than constituting three, narrow, water-tight and independent exceptions. This is illustrated in *Mayo* by the Court's reliance on cases falling into each of the three sub-components (*O'Reilly v. Morse*, 15 How. 62 (1854) with respect to laws of nature; *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S 127 (1948) and *Diamond v. Chakrabarty*, 447 U.S. 303 (1980) regarding natural phenomena; *Diamond v. Diehr*, 447 U.S. 303 (1981), *Parker v. Flook*, 437 U.S. 584 (1978), and *Bilski v. Kappos*, 130 S. Ct. 3218 (2010) each dealing with abstract ideas) to elucidate the central purpose underlying the exception. In fact, the *Mayo* Court held that two cases, *Diehr* and *Flook*, both of which relate to *abstract ideas*, were "most directly on point" in relation to the *law of nature* at issue in *Mayo*. (*Mayo* at 1298.)

Second, that underlying purpose behind the exception is to avoid the "danger that the grant of patents that tie up [the] use [of laws and principles] will inhibit future innovation premised upon them, a danger that becomes acute when a patented process amounts to no more than an instruction to 'apply the natural law,' or otherwise forecloses more future invention than the underlying discovery could reasonably justify." (*Mayo* at 1301, citations omitted.) The Court recognized that patent law must consider both the facilitative and inhibitory effects of patents so as to maximize innovation:

> Patent protection is, after all, a two-edged sword. On the one hand, the promise of exclusive rights provides monetary incentives that lead to creation, invention, and discovery. On the other hand, that very exclusivity can impede the flow of information that might permit, indeed spur, invention, by, for example, raising the price of using the patented ideas once created, requiring potential users to conduct costly and time-consuming searches of existing patents and pending patent applications, and requiring the negotiation of complex licensing arrangements. (*Mayo* at 1305).

Third, the exception flows from the policy inherent in the patent laws as passed by Congress, not from definitions and concepts deriving from particular branches of science ("[P]atent law's general rules must govern inventive activity in many different fields of human endeavor, with the result that the practical effects of rules that reflect a general effort to balance these considerations may differ from one field to another." *Mayo* at 1305.) Further, the Court acknowledged that, in applying the exception, the courts should not engage in evaluating the scientific subtleties of a field of technology, an evaluation that the courts are ill-equipped to investigate: "Courts and judges are not institutionally well suited to making the kinds of judgments needed to distinguish among different laws of nature. And so the cases have endorsed a bright-line prohibition against patenting laws of nature, mathematical formulas and the like, which serves as a somewhat more easily administered proxy for the underlying "building-block" concern." (*Mayo* at 1303.)

Fourth, the exception plays its role independently from any subsequent, substantive, investigations into novelty, non-obviousness or description. ("These considerations lead us to decline the Government's invitation to substitute §§ 102, 103, and 112 inquiries for the better established inquiry under § 101." *Mayo* at 1304.) "[T]o shift the patent-eligibility inquiry entirely to these later sections risks creating significantly greater legal uncertainty, while assuming that those sections can do work that they are not equipped to do." (*Mayo* at 1304.)

B. The Federal Circuit Ignored and Contradicted this Court's Test in *Mayo*

The majority in the Federal Circuit ignored each and every one of these holdings.

First, the Federal Circuit held that there are three separate and narrow exceptions, rather than one principled exception to patent eligibility: "The Court's precedents provide three judicially created exceptions to § 101's broad patent-eligibility principles." (App. at 42a) This leads the Federal Circuit to erroneously conclude that *Mayo*, which dealt with laws of nature, had no application to the composition-of-matter claims before the court. ("Mayo does not control the question of patent-eligibility of such claims." App. at 44a.) Instead, the Federal Circuit restricted its analysis to only two cases, *Chakrabarty* and *Funk Brothers*, thus failing to acknowledge the fundamental and common link between the exception to patent eligibility in all its forms. ("While *Mayo* and earlier decisions concerning method claim patentability provide valuable insights and illuminate broad, foundational principles, the Supreme Court's decisions in *Chakrabarty* and *Funk Brothers* set out the primary framework for deciding the patent eligibility of compositions of matter, including isolated DNA molecules." App. at 48a, citation omitted.)

Second and due to this error, the Federal Circuit not only ignored this Court's discussion of the underlying purpose of the exception in *Mayo* but flatly contradicted it. The Federal Circuit held the negative effects on further innovation and use of innovation caused by patents was not before them: "The question is also not whether is it desirable for one company to hold a patent or license covering a test that may save people's lives, or for other companies to be excluded from the market encompassed by such a patent—that is the basic right provided by a patent, i.e., to exclude others from practicing the patented subject matter." This opposes the clear statement in *Mayo* that this is, in essence, the primary motivation of the exception to patent eligibility in § 101. Because of this error, the Federal Circuit ignored the fact that the use of DNA in the disputed claims depended directly and uniquely on its informational function. ("The claimed isolated DNA molecules are distinct from their natural existence as portions of larger entities, and their informational content is irrelevant to that fact." App. at 55a.)

Third, rather than engaging in a discussion of balancing the positive and negative effects of patents on innovation, the Federal Circuit attempted to answer the question of patent eligibility based on a technical analysis of the phenomenon of nature at issue–DNA–despite this Court's admonition in *Mayo* that the judiciary is institutionally ill-equipped to engage in this analysis. Proving this Court's admonition, the Federal Circuit answered the question of patent eligibility based on a faulty scientific understanding of DNA. Among the clear scientific errors that the Federal Circuit made were the following:

- A privileging of *covalent* over other forms of chemical bonds when the function of DNA relies on *hydrogen* bonds; and

- Asserting that DNA molecules that are covalently separated from chromosomes (thus "isolated") are not found in nature, whereas DNA molecules not covalently bound to chromosomal DNA are commonly found within cells in the process of normal cell division and DNA repair.

The consequence of these scientific errors is a decision of the Federal Circuit that cannot be supported by either law or science.

Fourth, the Federal Circuit ignored this Court's holding in *Mayo* that the analysis under § 101 is logically and structurally independent from that under §§ 102, 103, and 112. For example, the Federal Circuit refused to examine the uses of DNA, which are very relevant to the question of the impact of the patent claims on future innovation, on the basis that such analysis should be exclusively undertaken under § 103: "Uses of chemical substances may be relevant to the nonobviousness of these substances or to method claims embodying those uses, but the patent eligibility of an isolated DNA is not negated because it has similar informational properties to a different, more complex natural material." (App. at 55a). The lack of understanding of the uses of DNA led the Court to narrowly assess the patent eligibility of DNA on the basis of its being a chemical and ignoring its critical biological functions and how those functions have an impact on innovation: "We recognize that biologists may think of molecules in terms of their uses, but genes are in fact materials having a chemical nature and, as such, are best described in patents by their structures rather than by their functions." (App. at 55a).

Collectively, these errors undermine this Court's holding in *Mayo* and threaten to eviscerate the importance of the § 101 exception to patent eligibility developed by the Court since the mid-1800s.

II. THE DECISION OF THE FEDERAL CIRCUIT INTRODUCES CONFUSION INTO AN IMPORTANT AREA OF FEDERAL LAW

The Federal Circuit introduced significant uncertainty into determinations of the patent eligibility of biological molecules under 35 U.S.C. § 101 of the Patent Act. As naturally occurring biological molecules are ubiquitous not only in clinical genetics but in the life sciences generally—including medicine, agriculture, aquaculture, tree biotechnology, industrial biotechnology and new forms of energy—the majority's decision sows confusion in a critical area of federal law with effects across many industries throughout the United States.

In particular, the majority in the Federal Circuit creates the following three forms of uncertainty:

1. It asserts an arbitrary and scientifically illegitimate defining boundary between the claimed invention and nature: the cleavage of a covalent bond (App. at 54a ("But a covalent bond is the defining boundary between one molecule and another").) There is nothing unique regarding the importance of covalent bonds in chemistry or biology. Indeed, other types of bonds—such as the hydrogen bonds linking base pairs on opposing DNA strands that are critical for both replication and transcription and the ionic bonds that link histones to the DNA backbone that are essential to transcription—are at least as important. Hydrogen bonds between purines and pyrimidines, in particular, are features of DNA structure that are taught in textbooks as essential to its biological function;

2. It sets out conflicting criteria to determine whether a claimed invention is "markedly different," as required by *Chakrabarty*, from its natural counterpart so as to constitute eligible

subject-matter under § 101. The majority opinion of Judge Lourie took the position that a structural difference between the claimed matter and natural product was sufficient to be "markedly different" whereas both the concurring opinion of Judge Moore and the dissent of Judge Bryson stated that the claimed matter must be both structurally and functionally different from a natural product to so qualify; and

3. It assesses patent eligibility of claims from the point of view of a person having ordinary skill in the art (PHOSITA) of chemistry rather than of genetics, despite the clear application of the claimed invention in the life sciences and the specific statement of the patent applicant.

A. Cleavage of a Covalent Bond as Test for Patent Eligibility Introduces Uncertainty

The majority of the Federal Circuit held that the claimed isolated DNA molecules were chemically distinct from DNA in the human body (App. at 53a) because Myriad had cleaved "a covalent bond [which] is the defining boundary between one molecule and another." (App. at 54a.) This argument introduces a test of patent eligibility under § 101—the breaking of covalent bonds— that is inappropriate and sows confusion in determining which naturally occurring biological molecules, in fields well beyond clinical human genetics, are eligible to be patented.

The Federal Circuit failed to provide a reason that covalent, rather than other types of bonds—in particular ionic and hydrogen bonds—are the features that distinguish what is patentable from that which is not patentable. The majority's only explanation is based on a fundamental misunderstanding of a seminal 1960s text on chemistry: "But a covalent bond is the defining boundary between one molecule and another, and the dissent's citation of Linus Pauling's comment that covalent bonds 'make it convenient for the chemist to consider [the aggregate] as an independent molecular species' underlines the point." (App. at 54a.)

The majority's misreading of Pauling actually proves the point opposite to that it was making. Pauling was talking of chemical bonds in general—which also include ionic and hydrogen bonds—rather than only covalent bonds. The actual quote from Pauling is "that there is a chemical bond between two atoms or groups of atoms in case that the forces acting between them are such as to lead to the formation of an aggregate with sufficient stability to make it convenient for the chemist to consider it as an independent molecular species." LINUS PAULING, THE NATURE OF THE CHEMICAL BOND AND THE STRUCTURE OF MOLECULES AND CRYSTALS: AN INTRODUCTION TO MODERN STRUCTURAL CHEMISTRY 6 (3d ed. 1960). Pauling defined chemical bond on the previous page as including "electrostatic bonds [which include both ionic and hydrogen bonds], covalent bonds and metallic bonds." *Id.* at 5.

Indeed, hydrogen bonds, and not covalent bonds, are the most important defining characteristic of DNA as they are responsible for the unique complementary structure of the double helix and for the manner in which the DNA is folded. In fact, one of the key discoveries to how DNA is copied in cells came from the discovery of naturally occurring DNA fragments that are not covalently bound to the DNA backbone but that are newly synthesized and held in place by hydrogen bonds. This natural synthesis occurs in the same way that, using the CAFC's definition of 'isolated', isolated DNA molecules are produced when using current DNA diagnostic methods. While covalent bonds certainly play an important role in biology, and provide DNA chemical stability as the repository of genetic information, other bonds are of greater significance in the field of genetics. The essence of DNA, its information-carrying capacity and its ability to replicate, is directly dependent upon hydrogen bonds that link the base pairs in opposing strands. It is an anti-symmetrical double helix precisely and only because of hydrogen bonds, not the covalent bonds in the backbone. Similarly, the ability of DNA to copy itself (replication) and the transcription of DNA into RNA rely on both hydrogen bonds and the ionic bonds connecting histones and DNA-binding proteins that turn on and off transcription.

Even the concurring opinion expressed doubt as to whether the cleavage of covalent bonds was sufficient to establish the patent eligibility of isolated DNA sequences: "If I were deciding this case on a blank canvas, I might conclude that an isolated DNA sequence that includes most or all of a gene is not patentable subject matter." (App. at 86a.)

The problem with the majority's decision is far deeper, however, than the arbitrariness with which it privileged the role of covalent bonds over other types of bond: the majority failed to provide a substantive rationale of why the cleavage of any bond should be the key to determining patent eligibility under § 101. It cited no cases to support this decision and failed to consider the effect of its novel test on the patentability of other naturally occurring biological molecules, such as proteins, and other naturally occurring structures, such as cell lines. Claims reading over isolated proteins would seemingly fail the majority's test, as no covalent bond would normally be cleaved during this process of isolation. This would have a profound effect not only in the limited area of human clinical genetics, but across all of biology from regenerative medicine (e.g., U.S. Patent No. 8,057,788 (filed Dec. 28, 2006), directed to placental stem cells, assigned to the Anthrogenesis Corporation of New Jersey); to agriculture (e.g., U.S. Patent No. 8,067,669 (filed Mar. 5, 2010), directed to a protein to inhibit soya rust, assigned to The University of Missouri); industrial applications (e.g., U.S. Patent No. 8,034,600 (filed Aug. 5, 2008), directed to a protein used in starch and alcohol production, cleansing and textiles, assigned to Danisco U.S. of California); and energy (e.g., U.S. Patent No. 8,004,264 (filed Sept. 23, 2008), directed to proteins that enhance the use of wood, agricultural crops and other organic materials into ethanol, assigned to Novozymes, Inc. of California).

None of this Court's decisions call for the bright-line test developed by the majority in the Federal Circuit. On the contrary, this Court has repeatedly warned against the use of arbitrary tests in the application of § 101 (see e.g., *Bilski*). The majority's decision violates this rule, introducing a test for patent eligibility that is not only unsupported by legislation, case law or scientific principle, but that creates significant uncertainty over the patent eligibility of a large range of naturally occurring biological molecules.

B. Conflicting Tests for Patentable Subject Matter under § 101

While the majority opinion found isolated DNA sequences to constitute patentable subject matter under § 101, the two members of the majority disagreed on the legal rule to be used in arriving at this decision, sowing further confusion for the application of this rule in the future.

Judge Lourie, in the majority decision, interpreted this Court's decision in *Chakrabarty* as drawing "a line between compositions that, even if arrayed in useful combinations or harnessed to exploit newly discovered properties, have similar characteristics as in nature, and compositions that human intervention has given 'markedly different,' or 'distinctive,' characteristics." (App. at 50a.) He then gave an interpretation of "markedly different" and "distinctive" that reduced the meaning of these terms to require a structural difference, even if not directly relevant to what renders the invention inventive: "We disagree, as it is the distinctive nature of DNA molecules as isolated compositions of matter that determines their patent eligibility rather than their physiological use or benefit." (App. at 55a.)

Both the concurring opinion and the dissent interpreted *Chakrabarty* more in line with its literal meaning, as requiring more than a mere structural difference between the claimed invention and naturally occurring DNA sequences. The concurring opinion noted that: "To the extent the majority rests its conclusion on the chemical differences between genomic and isolated DNA (breaking the covalent bonds), I cannot agree that this is sufficient to hold that the claims to human genes are directed to patentable subject matter." (App. at 81a-82a). Similarly, the dissent found that a claimed invention must exhibit both structural and functional differences from natural compositions of matter: "In sum, the test employed by the Supreme Court in *Chakrabarty* requires us to focus on two things: (1) the similarity in structure between what is claimed and what is found in nature and (2) the similarity in utility between what is claimed and what is found in nature." (App. at 110a.)

The result of these different opinions is that, while the majority opinion of the Federal Circuit held that structural differences between a naturally occurring biological compound and a claimed invention were sufficient to meet the requirements of § 101, a majority of judges found that a functional difference was also required. This mixed reasoning within the Federal Circuit establishes an incoherent and inconsistent set of rules for future courts attempting to apply § 101.

C. The Federal Circuit Relies on the Wrong PHOSITA

In *Ultramercial, LLC v. Hulu, LLC*, 657 F.3d 1323 (Fed. Cir. 2011), the Federal Circuit recognized the importance of providing context for a claim prior to an analysis of its patent eligibility under § 101. "On many occasions, however, a definition of the invention via claim construction can clarify the basic character of the subject matter of the invention. Thus, claim meaning may clarify the actual subject matter at stake in the invention and can enlighten, or even answer, questions about subject matter abstractness." Id. at 1325.

While the court in *Ultramercial* did not explicitly address whether claim construction for purposes of patent eligibility under § 101 follows the general rules of claim construction for patent infringement, its clear implication was that it did. Nevertheless, the majority in the Federal Circuit in the case under appeal chose not the PHOSITA in the field specifically noted by the patent applicant, nor a scientist in the life sciences (a geneticist or biochemist), but a chemist who would not be specifically knowledgeable about the invention, its utility or its import. In so doing, the majority created confusion in the construction of life science claims.

In the case under appeal, the Federal Circuit began the process of claim construction by situating the claims in light of the understanding that a chemist would bring to the claimed invention. "We recognize that biologists may think of molecules in terms of their uses, but genes are in fact materials having a chemical nature and, as such, are best described in patents by their structures rather than their functions." (App. at 55a.) Based on the understanding of a chemist, the majority held that: "Although isolated DNA is removed from its native cellular and chromosomal environment, it has also been manipulated chemically so as to produce a molecule that is markedly different from that which exists in the body." (App. at 52a.)

While the majority was correct in placing the claim within the context of a specific art to which it applies, it selected the wrong PHOSITA. As noted by the dissent: "If we are to apply the conventional nomenclature of any field to determine whether Myriad's isolated DNA claims are 'new,' it would seem to make more sense to look to genetics, which provides the language of the claims, than to chemistry." (App. At 105a.)

Further, the patent documents prepared by Myriad point directly to the field of genetics rather than to chemistry. In fact, the opening line in several sections, including the abstract and description, of U.S. Patent No. 5,747,282 (filed June 7, 1995) states: "The present invention relates generally to the field of human genetics."

The majority's error in selecting a PHOSITA permeates its decision. In particular, it leads the majority to the biologically incorrect conclusion that:

> It is undisputed that Myriad's claimed isolated DNAs exist in a distinctive chemical form—as distinctive chemical molecules—from DNAs in the human body, i.e., native DNA. Natural DNA exists in the body as one of forty-six large, contiguous DNA molecules. Each of those DNA molecules is condensed and intertwined with various proteins, including histones, to form a complex tertiary structure known as chromatin that makes up a larger structural complex, a chromosome. Inside living cells, the chromosomes are further encapsulated within a series of membranes and suspended in a complex intracellular milieu.
>
> Isolated DNA, in contrast, is a free-standing portion of a larger, natural DNA molecule. Isolated DNA has been cleaved (i.e., had covalent bonds in its backbone chemically severed) or synthesized to consist of just a fraction of a naturally occurring DNA molecule. For example, the BRCA1 gene in its native state resides on chromosome 17, a DNA

> molecule of around eighty million nucleotides. Similarly, BRCA2 in its native state is located on chromosome 13, a DNA of approximately 114 million nucleotides. (App. at 51a) (citations and cross-references omitted.)

The above conclusion ignores biological reality by assuming that native DNA exists *solely* in the form of large, contiguous chromosomes and that smaller strands of DNA are not natural. In fact, DNA naturally exists (for example during replication) within organisms in varying lengths that are much smaller than an entire chromosome, as assumed by the majority. DNA molecules smaller than an entire chromosome but corresponding to claimed DNA sequences (e.g., claims 5 and 6 of '282) commonly exist in nature. Such molecules are regularly created within cells during DNA replication and through normal mistakes in DNA transcription or through the cleavage of a covalent bond within the chromosome caused by radiation or a natural chemical agent. In fact, ironically, BRCA1 and BRCA2 proteins apparently play a role in repairing just such cleavages. See Serena L. Clark, Ana M. Rodriguez, Russel R. Snyder, Gary D.V. Hankins & Darren Boehning, *Structure-Function of the Tumor Suppressor BRCA1*, 1(1) COMPUTATIONAL AND STRUCTURAL BIOTECHNOLOGY JOURNAL e201204005 and Ashok R. Venkitaramen, Cancer Susceptibility and the Functions of BRCA1 and BRCA2, 108(2) CELL 171 (2002). That is, BRCA1/2 protein function is needed in cells precisely because sub-chromosomal DNA molecules with cleaved covalent bonds occur naturally.

Given the differences between a chemist and a geneticist in appreciating the biochemistry of the cell, the majority decision introduces significant confusion in determinations of patent eligibility under § 101.

CONCLUSION

Because of the uncertainty that the Federal Court injected into a critical area of federal law that extends across all of the life sciences as well as the conflict between the decision of the Federal Circuit and those of this Court, the petition for certiorari should be granted.

Respectfully submitted,

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AMICUS CURIAE BRIEF

Supreme Court, U.S.
FILED

OCT 31 2012

OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,
Petitioners,

v.

MYRIAD GENETICS, INC., ET AL.,
Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF *AMICI CURIAE* AMERICAN MEDICAL ASSOCIATION, AMERICAN SOCIETY OF HUMAN GENETICS, AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS, AMERICAN OSTEOPATHIC ASSOCIATION, AMERICAN COLLEGE OF LEGAL MEDICINE, AND THE MEDICAL SOCIETY OF THE STATE OF NEW YORK IN SUPPORT OF PETITION FOR WRIT OF CERTIORARI

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STATEMENT OF INTEREST OF *AMICI CURIAE*[1]

Genetic information is integral to physicians' determination of which diseases a patient might be suffering from and which treatments might benefit or harm that patient. Patents on human genes interfere with physicians' ability to provide appropriate care to their patients. These patents inhibit, rather than encourage, scientific research and technological innovation. They also contravene this Court's long-standing precedents about the scope of patentable subject matter.

Amici are organizations of health care professionals. Their members number in the hundreds of thousands and they provide health care across the country. *Amici* are concerned about the effect that the Federal Circuit's decision will have on the practice of medicine and on medical research. *Amici* urge the Court to grant certiorari and establish clearly that isolated DNA and cDNA are products of nature and therefore are not patentable subject matter and that the correlation between a potential therapeutic and cellular growth rate is an unpatentable law of nature.

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[1] No counsel for a party authored this brief in whole or in part, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No party or entity other than *amici*, their members, or their counsel, made a monetary contribution to this brief's preparation or submission. Counsel of record received timely notice of the intent to file this brief under Supreme Court Rule 37. Petitioners have filed a letter with the Clerk of the Court granting consent to the filing of any and all *amicus curiae* briefs. Respondents' consent has been filed with the Clerk of the Court.

***Amicus Curiae* American Medical Association (AMA)**, a non-profit organization, is the largest professional association of physicians, residents, and medical students in the United States, with over 217,000 members. The AMA joins this brief on its own behalf and as a representative of the Litigation Center of the American Medical Association and the State Medical Societies.

***Amicus Curiae* American Society of Human Genetics (ASHG)** is a non-profit organization of over 8,000 professionals in the field of human genetics including researchers, clinicians, academicians, and counselors.

***Amicus Curiae* American College of Obstetricians and Gynecologists (ACOG)** is a non-profit organization of over 51,000 health care professionals dedicated to providing quality health care to women. Over 90% of Board-certified obstetricians and gynecologists in the U.S. are affiliated with ACOG.

***Amicus Curiae* American Osteopathic Association (AOA)**, with over 44,000 members, is the largest professional association of osteopathic physicians. The AOA promotes osteopathic medicine, a holistic approach to prevent, diagnose, and treat illness, disease, and injury.

***Amicus Curiae* American College of Legal Medicine (ACLM)** is the nation's most prominent professional society comprised primarily of members holding degrees in both medicine and law. The ACLM serves medical and legal professionals and advises health policymakers.

***Amicus Curiae* Medical Society of the State of New York (MSSNY)** is a voluntary association of approximately 24,000 licensed physicians, residents, and medical students in all specialties in New York.

SUMMARY OF THE ARGUMENT

This Court has granted certiorari in cases of great social importance. Sup. Ct. R. 10. The question of whether genetic sequences are patent eligible is of far-reaching social importance—affecting patients, physicians, health care institutions, insurers, and researchers.

The patent claims at issue are of two types. Some cover "isolated DNA" and "cDNA," which are described by their genetic sequences, while others cover the correlation between potential therapeutics and cell growth. The enforcement of these patent claims impedes the provision of health care and shackles innovation.

Moreover, Myriad's patent claims conflict with this Court's jurisprudence on subject matter patent eligibility, which holds that "laws of nature, natural phenomena, and abstract ideas" are not patentable subject matter. *Mayo Collaborative Services v. Prometheus Labs,* 132 S. Ct. 1289, 1293 (2012).

This Court vacated the original opinion of the Court of Appeals for the Federal Circuit in this case and remanded the case for consideration in light of *Mayo v. Prometheus. Association for Molecular Pathology v. Myriad Genetics, Inc.,* 132 S. Ct. 1794 (2012). On remand, the Federal Circuit refused to apply the *Mayo* holding to the genetic sequence claims, indicating that the *Mayo* decision is only relevant to the laws of nature exception and not to the products of nature exception. *Association for Molecular Pathology v. United States Patent and Trademark Office,* 689 F.3d 1303, 1325 (Fed. Cir. 2012). Yet the rationales for both exceptions are the same and the same test for patentability is employed under both exceptions: whether a purported invention involves an inventive concept and is significantly different from nature. *Diamond v. Diehr*, 450 U.S. 175 (1981) (law of nature); *Diamond v. Chakrabarty*, 447 U.S. 303 (1980) (product of nature); *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948) (product of nature). Consequently, the *Mayo* holding is relevant to this case.

As a result of the Federal Circuit's refusal to properly analyze Myriad's patent claims in light of 35 U.S.C. § 101 and this Court's decision in *Mayo*, patient care and medical research will continue to be impeded to the detriment of patients and society. For these reasons, we respectfully request that the Court grant certiorari.

ARGUMENT

I. Physicians' and Researchers' Access to Genetic Sequences for Health Care and Research Is a Matter of National Importance and Urgency.

A person's genetic sequence holds a vast array of data relevant to his or her health. It can indicate a predisposition to disease, as well as provide guidance regarding what treatments might be beneficial (or risky) for that person. Genetic sequence information can mean the difference between life and death in the diagnosis and treatment of patients.

The benefits of genetic testing are not limited to people with rare diseases. Genetic factors contribute to the leading causes of death: cancers of all types, heart disease, hypertension, Alzheimer's, diabetes, susceptibility to infectious diseases (e.g. the flu), kidney disease, and asthma. Richard A. King, Jerome I. Rotter, and Arno G. Motulsky, The Genetic Basis of Common Diseases (2d ed. 2002). Even with respect to the narrow range of diseases that do not have a genetic component, genetic testing has a role in determining how well patients will metabolize and respond to proposed medications.

A. Patents Covering Genetic Sequences Interfere with Diagnosis and Treatment of Patients.

A patent on a genetic sequence grants the patent holder complete control over the use of that sequence. The holder can forbid health care providers from using even unpatented methods to learn the sequence of a patient's gene. The patent holder can extract whatever royalty it wants from the person who wants to learn about his or her genetic sequence. Gene patent holders have prevented physicians and laboratories from offering genetic testing for medical conditions such as breast cancer, hearing loss, Alzheimer's, Long QT syndrome, Canavan disease, leukemia, hemochromatosis, and neurodegenerative disorders. Secretary [of Health and Human Services]'s Advisory Committee on Genetics, Health, and Society, *Report on Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests*, 41-42 (2010) [hereinafter "SACGHS"]; Debra G.B. Leonard, *Medical Practice and Gene Patents: A Personal Perspective*, 77 Academic Medicine 1388 (Dec. 2002).

In this case, because Myriad has exclusive use of the BRCA1 and BRCA2 gene sequences, no woman can get an independent second opinion about her condition before deciding to have her healthy breasts or ovaries removed in order to avoid cancer. As a result, women may have their breasts or ovaries removed unnecessarily when they receive a false positive result on a BRCA1 or BRCA2 test because they do not have access to an independent confirmatory test. *See, e.g.*, Judy Peres, *Genetic Testing Can Save Lives – But Errors Leave Scars*, Chicago Tribune, September 26, 1999, at 1. Myriad's exclusive control of the BRCA1 and BRCA2 gene sequences also restrict men's access to diagnostic testing. Although BRCA mutations are rarer in men, a mutation does increase the risk of male breast cancer as well as prostate and pancreatic cancer.

Patents on genetic sequences have even led to the death of patients, as in the case of Long QT syndrome, a disorder of the heart's electrical system that is characterized by irregular heart rhythms and a risk of sudden death. The disease can be treated with an implanted defibrillator. A genetic sequence associated with Long QT was patented and assigned to the University of Utah Research Foundation. U.S. Patent No. 6,207,383. For a two-year period, the exclusive licensee did not offer diagnostic testing for Long QT syndrome. Other laboratories had the capability and willingness to assess whether patients had a potentially fatal mutation of the Long QT gene, but were prevented from doing so due to the patent on the genetic sequence. During this period at least one patient, a 10-year-old girl, died from undiagnosed Long QT syndrome. Her death could have been prevented had the isolated genetic sequence not been patented. *Stifling or Stimulating – The Role of Gene Patents in Research and Genetic Testing: Hearing Before the Subcommittee on Courts, the Internet and Intellectual Property of the House Judicary Committee*, 110th Congress 40 (2007) (statement of Dr. Marc Grodman).

The promise of pharmacogenomics—the ability to test a patient's genetic sequence to determine whether a treatment might be helpful or deadly—has also been undermined by the patenting of genetic sequences. A company filed for patent protection on a genetic sequence that indicates whether patients will benefit from its asthma drug. For the 20-year term of the patent, the company will not allow anyone to use the sequence to determine whether its drug will help or harm patients. Geeta Anand, *Big Drug Makers Try to Postpone Custom Regimens*, The Wall Street Journal, June 18, 2001, at B1. Even though such information is crucial to physicians and patients, the use of the sequence to identify people who would not benefit from a drug would diminish the market for the drug.

Patents on genetic sequences also interfere with multiplex testing, where the sequences of several genes (or even a person's entire genome) are tested at once. SACGHS at 49. For example, as many as 80 genes can indicate a predisposition to asthma. G. Malerba and P.F. Pignatti, *A Review of Asthma Genetics: Gene Expression Studies and Recent Candidates*, 46 Journal of Applied Genetics 93 (2005). For a complete diagnosis, all the relevant genetic sequences could be analyzed in one test. But genetic sequence patents preclude a single test from being used. Because some genetic sequence patents are exclusively licensed, a patient's tissue sample must be sent to multiple laboratories, increasing costs and introducing additional chances of error.

The technology exists to allow the sequencing of a person's entire genome, approximately three billion base pairs, including 20,000 genes, at an affordable rate. "The goal of completely sequencing a human genome for $1,000 is in sight." W. Gregory Feero, Alan E. Guttmacher, and Francis S. Collins, *Genomic Medicine – An Updated Primer*, 362 New England Journal of Medicine 2001, 2008 (2010). Whole genome sequencing offers the possibility of personalized medicine, where a patient can take preventive measures to minimize his or her risk for a wide range of genetic diseases. However, patents on genetic sequences impede the deployment of a whole genome analysis for patients. Sulston Decl. ¶ 38; Ledbetter Decl. ¶ 24. Testing all 20,000 of a person's genes at the Myriad BRCA rate would convert a test that could be done for $1000 to one that cost over $37 million. Applying even a seemingly modest royalty of $100 per gene would total an unaffordable $2 million per test. If the decision of the Court of Appeals for the Federal Circuit is upheld, physicians will be unable to provide meaningful results and comprehensive information from whole genome sequencing.

B. Patents Covering Genetic Sequences Impede Innovation.

Patents on "isolated" genetic sequences impede innovation. There is no way to "design around" these patents. Any research or diagnosis done on a gene from a patient's body is controlled by the patent holder because no research or diagnosis can be done without "isolating" the DNA from the body. Myriad has stopped research involving BRCA1 and BRCA2 at major universities such as Yale. Kimberly Blanton, *Corporate Takeover Exploiting the US Patent System*, Boston Globe Magazine, Feb. 24, 2002, at 10.

Myriad argues that patents are necessary to encourage innovation (such as the discovery and isolation of genetic sequences). Myriad Supp. Br. at 16-18 (Fed. Cir., June 15, 2012). But the majority of geneticists are willing to undertake the research to discover genes and develop genetic tests without the possibility of a patent. In fact, in a study of ASHG members, 61% of those in industry, 78% of those in government, and 77% of academic scientists stated that they disapproved of patenting DNA. Isaac Rabino, *How Human Geneticists in U.S. View Commercialization of the Human Genome Project*, 29 Nature Genetics 15 (2001).

Gene sequence patents are not necessary to incentivize the discovery of genes and the development of genetic tests. SACGHS, *supra*, at 30. "[P]atents were not needed to develop genetic tests for hearing loss, SCA [spinocerebellar atrophy], breast cancer, LQTS [long-QT syndrome], Canavan disease, and HH [hereditary hemochromatosis]. Indeed, all of these tests were on the market before the test offered by the relevant patent-rights holder." *Id.* at 31.

Rather than encourage innovation, genetic sequence patents stifle it. A survey of directors of laboratories that perform DNA-based genetic tests indicated that over half (53%) had been impeded from developing tests due to gene patents. Cho Decl. ¶ 10; Mildred K. Cho et al., *Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services*, 5 Journal of Molecular Diagnostics 3 (2003).

C. The Issue Is Also of National Importance Because of the Substantial Public Investment in the Discovery of Genetic Sequences.

"The Human Genome Project could easily be the most important organized scientific effort in the history of mankind." M. R. C. Greenwood and Rachel E. Levinson, *Expanding the Horizons of Biotechnology in the Twenty-first Century*, *in* Biotechnology: Science, Engineering, and Ethical Challenges for the Twenty-first Century 233-245 (Frederick B. Rudolph and Larry V. McIntire eds., 1996). The entire foundation of the Human Genome Project was built on taxpayer money, which was awarded to researchers to sequence genes. Over $1.8

billion was spent by the U.S. government and non-profit institutions on genomics in the year 2000 alone. Lori B. Andrews, *Harnessing the Benefits of Biobanks*, 33 Journal of Law, Medicine and Ethics 22, 30 n. 52 (2007).

Myriad did not "invent" the BRCA genes nor did it alone discover them. Its researchers were part of an international publicly-funded consortium sequencing the breast cancer gene. Myriad used over $5,000,000 of taxpayer money from the National Institutes of Health. Bryn Williams Jones, *History of a Gene Patent: Tracing the Development and Application of Commercial BRCA Testing*, 10 Health Law Journal 123, 131 (2002). Myriad also relied on the work of federal researchers from the National Institute of Environmental Health Sciences (also funded with taxpayer money) and researchers from other institutions. Rachel Nowak, *NIH in Danger of Losing Out on BRCA1 Patent*, 266 Science 208, 209 (1994).

Unlike other areas of innovation, the discovery of genetic sequences has been primarily funded by taxpayer funds. That alone gives this case major social importance. Everyone in this country has a stake in the outcome.

II. Myriad's Claims Are Invalid Under Section 101 Jurisprudence.

Nature's handiwork is excluded from patentability. *Mayo Collaborative Services v. Prometheus Labs*, 132 S. Ct. 1289, 1293 (2012); *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010). "'Laws of nature, natural phenomena, and abstract ideas' are not patentable." *Mayo*, 132 S. Ct. at 1293 (2012) (citations omitted). "[A] new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter." *Mayo*, 132 S. Ct. at 1293; *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) (citing *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)). Rather, a newly discovered natural phenomenon must be "treated as though it were a familiar part of the prior art." *Parker v. Flook*, 437 U.S. 584, 591-92 (1978); *See also Bilski*, 130 S. Ct. at 3230.

For over 150 years, this Court has held that products of nature are not patentable (*Chakrabarty*, 447 U.S. at 309), nor are isolated or purified products of nature (*American Wood-Paper Co. v. Fibre Disintegrating Co.*, 90 U.S. (23 Wall.) 566, 594 (1874)), nor are synthetic products that are not markedly different from what is found in nature (*Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 311 (1884)).[2]

Even when a newly-discovered law of nature or product of nature is novel, nonobvious, and useful, it is still unpatentable under Section 101. *Mayo*, 132 S. Ct. at 1304. Newton's law of gravity was novel and nonobvious when it was discovered. It has been useful in understanding our physical universe and has informed our engineering disciplines. Gold mined from the earth has uses ranging from ornamentation to medicine. Even though such discoveries may meet other criteria for patentability, Section 101 prohibits their patenting. Laws of nature and products of nature must be "free to all men" so as to encourage innovation and to reward only actual inventors. *Funk Bros.*, 333 U.S. at 130.

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[2] The Federal Circuit tries to undermine these precedents by characterizing them as having invalidated the patent claims due to novelty concerns (now codified as §102 concerns) rather than patent eligible subject matter concerns (now codified as §101 concerns). *Association for Molecular Pathology*, 689 F.3d 1326 n. 10. However, these cases were decided under the Patent Act of 1836, Ch. 357, 5. Stat. 117 (July 4, 1836), before either §101 or §102 existed. In fact, these are the precedents, along with cases like *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1 (1931), that led to the creation of §101 in the 1952 Patent Act.

In a patentability analysis, Section 101 is a separate and threshold analysis. *Mayo* 132 S. Ct. at 1304. To be valid, a claim involving a law of nature must have an "inventive concept" that makes the claim "significantly more" than the law of nature. *Id.* at 1294 (citing *Flook*, 437 U.S. at 594; *Bilski*, 130 S. Ct. at 3230). Similarly, a claim involving a product of nature must have an inventive concept that involves significantly more than describing the product of nature. The claimed invention must be "markedly different" from what occurs in nature. *Chakrabarty*, 447 U.S. at 310. *See also Funk Bros.*, 333 U.S. at 130 (1948); *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1, 11-12 (1931); *Cochrane*, 111 U.S. at 311; *American Wood-Paper Co.*, 90 U.S. (23 Wall.) at 594.[3]

Section 101 assures that innovators in our society—including physicians and scientists—have access to the raw materials for innovation. Laws of nature and products of nature are the "basic tools of scientific and technological work." *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972). Innovation is enhanced when all researchers have access to these basic tools.

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[3] This test is no more difficult to apply than any other analysis of patentability. If an inventor patents one type of mousetrap and another inventor files for a patent on another type of mousetrap, a judgment must be made about whether the second mousetrap involved an inventive concept and was markedly different from the prior art (the first mousetrap). In the application of Section 101, a similar analysis is made. But in that case the prior art is the product of nature itself.

The patent claims at issue in this case, covering isolated DNA and cDNA, which are described by their genetic sequences, are invalid because they are patents on products of nature without an inventive concept and because isolated DNA and cDNA are not markedly different from what occurs in nature in every human being. Similarly, correlations between treatments and cell growth are unpatentable laws of nature. If gene discoverers want to exempt themselves from the application of Section 101, their remedy is with Congress, not the courts.

A. Isolated DNA Is an Unpatentable Product of Nature.

Myriad's isolated genetic sequence claims do not involve an "inventive concept" and are not "markedly different" from the genetic sequence as it occurs in nature. The term "isolated" adds nothing of significance to the genetic sequence claims because isolation of genetic sequences is a well-understood conventional activity engaged in by geneticists. *See Mayo*, 132 S. Ct. at 1298.

When Myriad's counsel was pressed to identify its inventive concept at oral argument on remand, Myriad's main argument was that the decision of the scientist about where to "cut" the gene sequence to remove it from the chromosome was the inventive concept. Fed. Cir. Oral Arg. on Remand Trans. at

42:48 (July 20, 2012). Under such logic, the first surgeon who successfully removed a kidney for transplant, because he decided where to cut, could obtain a composition of matter patent covering all kidneys later removed by anyone else.

Nor does the breaking of covalent bonds make isolated DNA patentable. The change in chemical bonds is insignificant because the isolated genetic sequence is the same string of nucleotides that exists in the cell. In fact, the sequences patented by Myriad would be of no use in diagnosis or treatment if they were different from the sequences that occur naturally in the human body. Additionally, because the claims are written in terms of the genetic sequences, patentability should be determined by an analysis of the genetic sequence, not by the chemical structure.

B. cDNA Is an Unpatentable Product of Nature.

cDNA is useful in the laboratory because it has the same nucleotide sequence and contains the same information as the coding regions of naturally occurring genes and can perform the same functions as a full genetic sequence or DNA molecule. Bruce Alberts et al., Molecular Biology of the Cell 469-546 (4th ed. 2002).

Myriad's use of routine chemical tools to synthesize cDNA lacks the inventive concept necessary for patentable subject matter. cDNA is not "markedly different" from the sequence as it occurs within the chromosome. As this Court held in *Cochrane* with regard to a synthetic version of a dye, "[c]alling it artificial alizarine *did not make it a new* *composition of matter, and patentable as such, by reason of its having been prepared artificially*." 111 U.S. at 311 (emphasis added).

Once the gene's naturally occurring DNA sequence—an unpatentable product of nature—is known, synthesis of cDNA is a routine mainstay of the art of biologists and chemists. Allowing a patent on cDNA would be a disproportionate reward in relation to what the alleged inventor contributed.

C. The Method Described in Claim 20 Is Unpatentable Subject Matter.

Claim 20 of U.S. Patent No. 5,747,282, like the invalid claims in *Mayo*, 132 S. Ct. at 1290-1291, consists of (1) an "administering" step (where a cell containing an altered BRCA1 gene causing cancer is grown in the presence of a potential therapeutic compound); (2) a "determining" step (where the growth of the cell with the potentially therapeutic compound is compared to the growth of a control cell); and (3) a "wherein" step (describing that a slower growth of the cell in the presence of a compound indicates a cancer therapeutic).

The "administering" step in claim 20, like the administering step in *Mayo*, only serves to identify who would be interested in the correlation: physicians. The "determining" step in *Mayo* tells the physician to measure the patient's metabolite levels using routine methods. *Id.* Similarly, the "determining" step in claim 20 tells the physician or researcher to measure the growth of the cells—a routine activity for physicians and scientists in the field. The "wherein" step in both instances simply tells the physician or researcher about the relevant law of nature. For the same reason that the claims in *Mayo* were invalid as claiming a law of nature, this Court should grant certiorari and hold that claim 20 is invalid.

D. Myriad's Contributions Do Not Justify the Threat to Innovation.

In a Section 101 analysis, courts need to weigh "how much future innovation is foreclosed relative to the contribution of the inventor." *Mayo*, 132 S. Ct. at 1303. Indeed, "[t]he reason for the exclusion is that sometimes *too much* patent protection can impede rather than 'promote the Progress of Science and useful Arts,'" *Laboratory Corp. of America Holdings v. Metabolite Labs., Inc.*, 126 S. Ct. 2921, 2922 (2006) (J. Breyer, dissenting). In *O'Reilly v. Morse*, this Court held that by patenting all uses of electromagnetism to produce characters at a distance, "while he shuts the door against inventions of other persons, the patentee would be able to avail himself of new discoveries in the properties and powers of electro-magnetism which scientific men might bring to light." 56 U.S. (15 How.) 62, 113 (1853). In this case, Myriad can improperly avail itself of all later discoveries related to human breast cancer genetic diagnosis and treatments, disproportionate to its efforts.

Myriad's contribution to the sequencing and identification of the BRCA1 and BRCA2 genes was minor in comparison to what its patents foreclose. Myriad used common techniques to isolate, sequence, and clone the BRCA1 and BRCA2 genes. Further, Myriad did not identify the sequences on its own.

Myriad had significant scientific aid and financial support, including from taxpayer funds.

Myriad not only patented the entire genetic sequence of BRCA1 and of BRCA2, but also every sequence of 15 nucleotides that appears in the BRCA1 genetic sequence. *See* claims 5 and 6 of '282 patent. These sequences appear hundreds of thousands of times in the 3 billion base pairs of the human genome. Myriad now can demand a royalty for the use of numerous genetic tests that have nothing to do with breast cancer because those sequences of 15 nucleotides occur in so many places in the genome. There are 340,000 infringing sequences on Chromosome 1 alone. Thomas Kepler, Colin Crossman, Robert Cook-Deegan, *Metastasizing Patent Claims on BRCA1*, Genomics (2010). Since those 15 nucleotide sequences occur an average of 14 times per gene, Myriad could ask for a royalty on every test done on any gene. Myriad could hold the deployment of whole genome sequence testing hostage by threatening to pursue an infringement action for every instance one of those 15 nucleotide segments is sequenced.

E. The Federal Circuit Did Not Adequately Apply This Court's Precedents.

On remand, the Federal Circuit failed to adequately consider Section 101 and *Mayo*.[4] This

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[4] On remand, the Federal Circuit issued an opinion nearly identical to its original opinion in reasoning, wording and length. A track change comparison shows how little deference the court gave to *Mayo* and how little the Federal Circuit's second decision differed from its first decision. John Conley and

Court has repeatedly stated that "laws of nature, natural phenomena, and abstract ideas" are excluded from patentability and has treated all three exceptions in the same manner. *Mayo*, 132 S. Ct. at 1293 (citing Diamond *v. Diehr*, 450 U.S. 175, 185 (1981)). Yet, Judge Lourie, writing for the majority, held that since a gene sequence is not a "law of nature," the teachings of *Mayo* do not apply. *Association for Molecular Pathology*, 689 F.3d at 1325, 1333. The Federal Circuit's approach is inconsistent with this Court's precedents which apply Section 101 to both laws of nature and products of nature. *Diehr*, 450 U.S. 175 (law of nature); *Funk Bros.*, 333 U.S. 127 (product of nature); *Chakrabarty*, 447 U.S. 303 (product of nature). Judge Lourie failed to realize that the law of nature exception is identical to the products of nature exception and thus the teachings of *Mayo* are relevant to this case.

Moreover, the Federal Circuit ignored its own precedents in holding that genetic sequences are patentable. The Federal Circuit elsewhere has correctly recognized that a patent cannot be granted to an applicant who has discovered a natural attribute of an entity. *In re Cruciferous Sprout Litigation*, 301 F.3d 1343 (Fed. Cir. 2002). In that case, the Federal Circuit stated, "[T]he glucosinolate content and Phase 2 enzyme-inducing potential of sprouts necessarily have existed as long as sprouts themselves, which is certainly more than one year before the date of application . . . ." *Id.* at 1350. Here,

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Dan Vorhaus, *Applying Mayo to Myriad: Latest Decision Brings No New News*, Genomics Law Report, Aug. 17, 2012, http://www.genomicslawreport.com/index.php/2012/08/17/applying-mayo-to-myriad-latest-decision-brings-no-new-news/#more-6807.

the valuable attributes of a gene sequence—the ability to anneal to a complementary strand for diagnosis and to produce proteins—are inherent in the sequence itself and are not caused by anything the supposed inventor did.

In *Aventis Pharma Deutschland GMBH v. Lupin, Ltd.*, 499 F.3d 1293 (Fed. Cir. 2007), the Federal Circuit found patent claims to an isolated chemical compound with therapeutic properties to be invalid, holding that "[i]solation of interesting compounds is a mainstay of the chemist's art," and that "[i]f it is known how to perform such an isolation doing so 'is likely the product not of innovation but of ordinary skill and common sense.'" *Id.* at 1302 (citing *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)). Yet in the case at bar, the Federal Circuit held that Myriad's patents on isolated gene sequences were valid, despite the isolation of gene sequences being the mainstay of the biologist's art.

Under the Federal Circuit's analysis, even the elements of the periodic table would be patentable. Indeed, Myriad's Counsel at oral argument admitted that the element lithium would be patentable if Myriad's view of the products of nature doctrine prevailed. Fed. Cir. Oral Arg. Trans. at 1:07:28 (Apr. 4, 2011). Such a travesty would conflict with past precedents that hold that the elements of the periodic table are not patentable. *General Electric Co. v. DeForest Radio Co.*, 28 F.2d 641 (3rd Cir. 1928), *cert. denied*, 278 U.S. 656 (1929)(isolated tungsten); *In re Marden* (Marden I), 47 F.2d 957 (C.C.P.A. 1931)(isolated uranium); *In re Marden* (Marden II), 47 F.2d 958 (C.C.P.A. 1931)(isolated vanadium).

III. The United States Patent and Trademark Office Erred in Granting Genetic Sequence Patents and Its Erroneous Decision Should Not Be Given Deference.

The United States Patent and Trademark Office (USPTO) ignored this Court's precedents and applied flawed reasoning to permit patents on genetic sequences. Consequently, that reasoning should not be accorded deference. The USPTO relied on the 1873 grant of a patent to Louis Pasteur for a purified yeast and on a 1911 lower court decision upholding a patent for isolated and purified adrenaline. *Utility Examination Guidelines*, 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001); *Parke-Davis & Co. v. H. K. Mulford Co.*, 189 F. 95 (S.D.N.Y. 1911), *affirmed*, 196 F. 496 (2d Cir. 1912). However, the Pasteur patent and *Parke-Davis* preceded this Court's decision in *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1 (1931). That decision elaborated on the products of nature doctrine in a way that calls into question the grant of the yeast patent and adrenaline patent. Indeed, no less an authority than Pasquale J. Federico (later Commissioner of Patents and principal drafter of the 1952 Patent Act, which includes Section 101) stated that in light of *American Fruit Growers*, a claim like Pasteur's "would now probably be refused by the examiner, since it may be doubted that the subject-matter is capable of being patented." Pasquale J. Federico, *Louis Pasteur's Patents*, 86 Science 327 (1937).[5] Thus, the USPTO erred when it began granting patents on genetic sequences.

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[5] The Pasteur patent might not even have been valid according to the law at the time it was issued. Since Pasteur never enforced his patent, there was no judicial assessment of whether the patent was valid. Maurice Cassier, *Louis Pasteur's*

The Federal Circuit compounded this error by looking to *Parke-Davis* in assessing the genetic sequence claims. *Association for Molecular Pathology*, 689 F.3d at 1329; *see also id.* at 1339 (Moore, J., concurring-in-part). Judge Moore additionally cited the discredited Pasteur patent as precedent. *Id.* at 1344 (Moore, J., concurring-in-part).

The Federal Circuit also held that the USPTO's actions created "settled expectations" that prohibited the Federal Circuit from holding genetic sequence claims invalid. *Id.* at 1332; *see also*, *id.* at 1366-1367 (Moore, J., concurring-in-part). However, allowing settled expectations to dictate the validity of a patent would lead to absurd results. The examiners at the USPTO are not infallible. Sometimes whole categories of claims have been erroneously included or excluded from patentability. In fact, in a study of challenges to patent validity, 46% of challenged patents were found to be invalid. John R. Allison, Mark A. Lemley, *Empirical Evidence on the Validity of Litigated Patents*, 26 QIPLA Q.J. 185 (Summer 1998).

If the USPTO were owed the level of deference that the Federal Circuit proposes, there would be no recourse to challenge invalid patents. Anytime a court reviews a patent there is a chance to change settled expectations. In *State Street Bank & Trust Co v. Signature Financial Group, Inc.*, 149 F.3d 1368 (Fed. Cir. 1998), the Federal Circuit changed the

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Patents: Agri-Food Biotechnologies, Industry and Public Good, *in* Living Properties, 39 (Jean-Paul Gaudillière, *et al.*, eds., 2009).

settled expectation of business owners who had previously felt free to use business methods without concern for patent infringement. As is clear in *Mayo*, settled expectations do not provide an adequate reason for courts to uphold otherwise invalid patents.

Furthermore, the U.S. Government asked the Federal Circuit not to give deference to the USPTO's practice of granting patents on isolated DNA. The Department of Justice submitted an *amicus* brief in the Federal Circuit arguing that isolated DNA is a product of nature and not patentable subject matter. Brief for the United States as *Amicus Curiae* in Support of Neither Party 11, *Association for Molecular Pathology* (Fed. Cir., Oct. 29, 2010).

> The chemical structure of native human genes is a product of nature, and it is no less a product of nature when that structure is 'isolated' from its natural environment than are cotton fibers that have been separated from cotton seeds or coal that has been extracted from the earth.

IV. Invalidation of Myriad's Patent Claims Is Not Only Required by Section 101, It Is Consistent with Scientific and Medical Ethics Codes.

Scientists have long-standing, historically recognized duties to freely disseminate their discoveries of products of nature and laws of nature and not to subject those discoveries to private property rights. *See, e.g.*, Robert K. Merton, On the Shoulders of Giants: A Shandean Postscript (1985).

Medical professionals, too, recognize the ethical duty to share scientific knowledge rather than to patent it.

As *Amicus* AMA's Ethics Opinion 9.095 states, "The use of patents, trade secrets, confidentiality agreements, or other means to limit the availability of medical procedures places significant limitation on the dissemination of medical knowledge, and is therefore unethical." American Medical Association, Opinion 9.095 – The Use of Patents and Other Means to Limit Availability of Medical Procedures (adopted June 1995), www.ama-assn.org/ama/ pub/physician-resources/medical-ethics/code-medical-ethics/opinion 9095.shtml. Similarly, *Amicus* ACOG's ethics opinion finds medical and surgical patents to be unethical and urges that genetic sequence patents not be granted. The American College of Obstetricians and Gynecologists, *ACOG Committee Opinion Number 364: Patents, Medicine, and the Interests of Patients*, 109 Obstetrics & Gynecology 1249, 1252 (2007, reaffirmed 2009).

Just as patent law recognizes that discoveries of nature must be widely shared to promote innovation, physicians' and scientists' ethical duties recognize that laws of nature and products of nature must be treated as prior art and shared to benefit the public and to encourage innovation.

CONCLUSION

An assessment of the validity of the patent claims at issue in the case is of great social importance. Patents on genetic sequences and patents on correlations between therapeutics and cell growth thwart patient care and hinder innovation. They also are invalid under Section 101. For these reasons, this Court should grant certiorari.

Respectfully submitted,

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October 30, 2012

AMICUS
CURIAE
BRIEF

Supreme Court, U.S.
FILED
OCT 31 2012
OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR CANAVAN FOUNDATION, CLAIRE ALTMAN HEINE FOUNDATION, MARCH OF DIMES FOUNDATION, FACING OUR RISK OF CANCER EMPOWERED, NATIONAL ASSOCIATION FOR PSEUDOXANTHOMA ELASTICUM, AND OVARIAN CANCER NATIONAL ALLIANCE AS *AMICI CURIAE* IN SUPPORT OF PETITIONERS

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U.S. DEP'T OF HEALTH & HUMAN SRVS., SECRETARY'S ADVISORY COMMITTEE ON GENETICS, HEALTH, & SOCIETY, GENE PATENTS AND LICENSING PRACTICES AND THEIR IMPACT ON ACCESS TO GENETIC TESTS (2010) 10

STATEMENT OF INTEREST OF *AMICI CURIAE*[1]

Each of the patient groups who submit this Amicus Brief have a direct and immediate need for the Court to address the issues in this patent case and to correct the errors in the analysis and decision produced in this matter by the U.S. Court of Appeals for the Federal Circuit.

Canavan Foundation is a non-profit organization with the mission to provide funding for research efforts to find an effective therapy for, raise awareness of, and to help avoid Canavan disease through carrier screening and prenatal testing. Despite efforts to sponsor low cost screening for potential carriers of Canavan's disease, a doctor and hospital who patented the relevant gene have prevented the group's efforts to provide free or inexpensive screening programs.

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[1] No counsel for a party authored this brief in whole or in part, and no such counsel or a party made a monetary contribution intended to fund the preparation or submission of this brief. No party or entity other than amici, their members, or their counsel, made a monetary contribution to this brief's preparation or submission. Counsel of record received timely notice of the intent to file the brief under Supreme Court Rule 37. Petitioners have filed a letter with the Clerk of the Court granting consent to the filing of any and all amicus curiae briefs. Respondents' letter granting amici consent to file has been filed with the Clerk of the Court.

Claire Altman Heine Foundation (CAHF) is a non-profit organization dedicated to establishing pan-ethnic carrier screening for Spinal Muscular Atrophy (SMA)—the number one genetic killer of children under two. In CAHF's experience, the use of patent rights relating to the gene responsible for SMA has reduced access to SMA carrier screening.

Facing Our Risk of Cancer Empowered (FORCE) is a non-profit organization whose mission includes providing people with information and resources to determine whether they are at high risk for breast and ovarian cancer due to family history or genetic predisposition.

March of Dimes Foundation is a non-profit organization dedicated to improving the health of babies by preventing birth defects, premature birth and infant mortality. March of Dimes' mission and research are adversely affected by patents on gene sequences.

National Association for Pseudoxanthoma Elasticum (NAPE) is a non-profit organization and the original Pseudoxanthoma Elasticum (PXE) patient support group in the United States, committed to providing education for afflicted individuals and families. NAPE opposes gene patents because they interfere with research and development of diagnostic and therapeutic tools.

Ovarian Cancer National Alliance (OCNA) is a non-profit organization and the foremost advocate for women with ovarian cancer in the United

States. OCNA opposes gene patents because such monopolies impede research on ovarian cancer and restrict access to genetic testing for the disease.

SUMMARY OF THE ARGUMENT

The central issue of this case is whether human genetic material, or a segment of the human genome, upon isolation and/or extraction from the body, constitutes patent eligible subject matter as defined in 35 U.S.C. § 101 . To be clear, the patents now at issue do not claim a means of isolating or extracting the gene; they claim the gene itself as invention. The U.S. District Court held that the genes as defined in the patent claims are "products of nature" and fall squarely within the judicially recognized exceptions to patentable subject matter. On appeal, the Federal Circuit panel affirmed the lower court's invalidation of all but one of Myriad's method claims but reversed its invalidation of composition claims holding that the genetic sequences themselves were patent eligible. The panel was divided and produced three separate opinions, including one concurrence and one dissent. Writing for the majority, Judge Lourie concluded that the mere *isolation* of a gene sequence was alone sufficient to qualify the genetic material as a product of human invention, despite the fact that the nucleotide sequence of the gene had not been altered, added to, reduced, or manipulated in any way.

On Plaintiffs' first Petition, this Court issued an order granting certiorari, vacating the Federal Circuit's decision and remanding this case to the

Federal Circuit for further proceedings in light of this Court's decision in *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012) . On remand, the same Federal Circuit panel affirmed its previous decision and issued a new set of opinions that are substantially identical to those issued previously. This result is unsurprising in view of the fact that the majority declared this Court's *Mayo* decision categorically irrelevant to composition of matter claims at issue in *Myriad*. Accordingly, the post-remand decision of the Federal Circuit does nothing to resolve the conflicting court opinions over this important issue of patent law.

Gene patents create a monopoly over information that is foundational for biological and medical sciences. By authorizing such monopolies, the Federal Circuit's decision sets a precedent that impedes research and innovation in the natural sciences. It is therefore inimical to the goals of innovation and growth for which the U.S. patent laws were designed.

In addition to its deviation from this Court's jurisprudence on fundamental issues affecting the scope and purpose of patent law, the Federal Circuit's decision authorizes patent practices that will severely compromise efforts in the U.S. to diagnose and treat chronic and life threatening diseases. The adverse effects of gene patents on science and healthcare are profound and wide ranging.

As the patient groups who submit this brief are keenly aware, the Federal Circuit's decision not only subverts the constitutionally grounded purposes of the patent laws but ushers in a set of commercial practices that are injurious to the health and welfare of U.S. citizens. For these reasons, we urge the Court to grant Petitioner's request for Writ of Certiorari.

ARGUMENTS IN SUPPORT OF REVIEW

I. THIS CASE HAS PROFOUND AND FAR REACHING CONSEQUENCES FOR MEDICAL SCIENCE, THE QUALITY OF AND ACCESS TO HEALTH CARE, AND THE LIVES OF PATIENTS AND THEIR FAMILIES

This case exemplifies how too much patent protection can impede our collective efforts to minimize the pain and suffering caused by fatal diseases. Patents like those at issue raise testing costs and simultaneously impede the development of more accurate and reliable diagnostic tools. The results are concretely and tragically experienced by patients and their families whose suffering might have been minimized or prevented altogether by more effective and less expensive means of testing for the genetic disposition to certain life threatening diseases. It is therefore no exaggeration to say that the consequences of affording patent protection to human genes can be lethal.[2]

Advocates of gene patenting, such as the Respondent, argue that upholding the district court's opinion would impede innovation and compromise patient diagnosis and treatment. But there is no factual support for those assertions. To the contrary, unless the district court's decision is upheld, the result will be less research, deficiency in diagnosing diseases, and worse outcomes for patients. The adverse consequences of gene patents are no longer speculative; there is ample empirical evidence of their detrimental effects.

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[2] *See infra* pp. 11-12.

A. *Adverse Consequences of Myriad's Patents*

As a consequence of its patents, Myriad gained the *exclusive right* to perform genetic testing and research on the BRCA1 and BRCA2 genes in the United States. But, when one party such as Myriad controls all testing of a gene sequence, it has no incentive to develop further knowledge of gene mutations affecting the risk of breast cancer or improve the quality of testing. Indeed there are several scientific studies that demonstrate the significant limitations of Myriad's test.[3] According to one study published in 2006, the test Myriad employs to detect breast cancer risk does not take into account significant possible mutations of the gene that correlate with a susceptibility to breast cancer. Tom Walsh et al.,

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[3] *See* Maurizia Dalla Palma et al., *The Relative Contribution of Point Mutations and Genomic Rearrangements in BRCA1 and BRCA2 in High-Risk Breast Cancer Families*, 68 Cancer Research 7006, 7011 (2008) (finding 8% of non-Ashkenazi Jewish test subjects carried a BRCA mutation not detectable by Myriad's standard test); Allison W. Kurian et al., *Performance of BRCA1/2 Mutation Prediction Models in Asian Americans*, 26 J. Clinical Oncology 4752, 4754-56 (2008) (finding that the models used by Myriad underestimate the prevalence of BRCA1/2 mutations among Asian American women by a full 50%).

Spectrum of Mutations in BRCA1, BRCA2, CHEK2, and TP53 in Families at High Risk of Breast Cancer, 295 J. Am. Med. Ass'n 1379, 1379-1388 (2006). In the study, researchers sampled DNA from 300 members of high-risk families that had received negative test results from Myriad. *Id.* The researchers used six methods to search DNA for breast cancer gene mutations, and found that 12% of the patients studied carried rearrangements of BRCA1 or BRCA2 that were not included in Myriad's array. *Id.*[4] Despite this and other empirical evidence that Myriad's test is deficient and often produces ambiguous results even with the mutations it checks, Myriad, as a result of its DNA sequence patents, remains in sole control of how or whether any new research on the BRCA genes will be conducted and/or incorporated into the tests that it offers.

B. *Adverse Effects of Gene Patenting Generally*

Myriad's patents provide but one example of the adverse effects on innovation of patents that preempt natural phenomena. In April 2010, the U.S. Department of Health and Human Services issued the Secretary [of Health and Human Services]'s Advisory Committee on Genetics,

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[4] The number of missed mutations may be even higher. According to Institute Curie geneticist Dr. Dominique Stoppa-Lyonett, Myriad's test may miss up to 20% of the expected BRCA1 mutations. Steve Benowitz, *French Challenge to BRCA1 Patent Underlies European Discontent*, 94 J. Nat'l Cancer Inst. 80, 80 (2002).

Health, and Society, Report on Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests (2010) [hereinafter "SACGHS"]. The report found that research in the field of genetics has already begun to suffer as a consequence of gene patents. "Patents are already hindering the development of multiplex tests. Laboratories utilizing multiplex tests are already choosing not to report medically significant results that pertain to patented genes for fear of liability." SACGHS at 3. As a consequence of their chilling effects on genetic research, the existence and enforcement of gene patents discourage the development of better quality testing methods. "Neither sample sharing nor competition is possible when an exclusive-rights holder prevents others providing testing. As a result, significant concerns about the quality of a genetic test arise when it is provided by a patent protected sole provider." SACGHS at 4.

Perhaps most directly and immediately of concern to the groups who submit this brief, the practice of patenting human genetic material has already proven to increase the costs of diagnostic procedures, restrict patient access to existing genetic testing, and preclude the availability of better tests and of second opinions of the often ambiguous results of current testing methods. *See* SACGHS at 1-6.

C. *Salient Cases of Individual Hardship*

There can be no doubt that patents on human genes worsen patient outcomes. The harm that can result from patenting human genes is dramatically illustrated in the case of familial Long QT syndrome (LQTS), a disorder of the heart's electrical system that affects 1 in 3,000 newborns and can result in sudden death. Misha Angrist, et al, *Impact of Patents and Licensing Practices on Access to Genetic Testing for Long QT Syndrome*, SACGHS at Appendix A, F-1. The disease has been correlated to mutations within three particular genetic sequences. *Id.* A company obtained a patent and exclusive license to the mutated genes for purposes of offering a diagnostic test but did not do so for two years because the exclusively-licensed laboratory went into bankruptcy. *Stifling or Stimulating – The Role of Gene Patents in Research and Genetic Testing: Hearing Before the Subcomm. on Courts, the Internet and Intellectual property of the H. Comm. on the Judiciary*, 110th Congress 35 (2007) (statement of Dr. Marc Grodman). During that time, the company nevertheless sought to enforce the patent against other parties who could have provided genetic testing for LQTS. *Id.* at 40. In the case of at least one patient, a ten year-old girl named Abigail who presented with an arrhythmia, death was preventable. *Id.* If the patent holder had made testing available, the cause of Abigail's arrhythmia would have been identified as LQTS, and the appropriate therapies could have been prescribed, such as beta-blocker drugs, implantable cardioverter-defibrillators, and avoidance of certain arrhythmia triggers. *Id.* ; Angrist, SACGHS at Appendix A, F-1.

In another well publicized case, Ashkenazi Jewish families of children with Canavan disease and non-profit foundations provided tissue and money for over a decade to a geneticist so that he could sequence the genetic mutation that caused this devastating neurological disease. The purpose was to provide a low cost screening and prenatal testing program for identifying potential carriers of the disease. Unfortunately, when the doctor identified the relevant gene sequence for carriers of the mutation, he and his hospital patented it without the knowledge or consent of the tissue sources. *See Greenberg v. Miami Children's Hosp. Research Inst., Inc.*, 264 F. Supp. 2d 1064 (S.D. Fla. 2003). When the Canavan Foundation and its constituents convinced medical providers to offer Canavan gene testing for free, the hospital threatened to enforce its patent and shut down the free testing.

D. *The Practice of Gene Patenting Discourages Patient Participation, and Thereby Limits the Fundamental Resource for Genetic Research*

Patient concern over the ultimate use of their personal tissue samples and genetic information has become a serious issue in genetic research. Patients have sued to stop use of their biological and genetic material in light of patent-holders' financial gain, undisclosed later uses, and restrictive licensing practices. *See Moore v. Regents of the Univ. of Cal.*, 793 P.2d 479 (Cal. 1990); *Greenberg*, 264 F. Supp. 2d 1064 ; *Washington Univ. v. Catalona*, 490 F.3d 667 (2007). Ignoring the role of patients in genetic research and innovation discourages patient participation, "the only irreplaceable, critical resource . . . in the discovery of [a] gene." Jon Merz, *Discoveries: Are There Limits on What May Be Patented?*, WHO OWNS LIFE? (2002).

The Canadian College of Medical Geneticists' official statement on gene patents addresses the needs of patients and other research participants who donate their time and personal biological samples "altruistically with a motivation to promote better care for others." Julie Richer et al., *CCMG statement on gene patents*, 82 CLIN. GENET. 405-407 (2012). Granting a patent to a single individual or entity in effect "fails to recognize the essential public investment in this process of collaboration and discovery . . . [and] fails to respect the wishes of patients who generously contribute with the hope of helping others," an oversight that "may have damaging effects on the future of genetic medicine by limiting the willingness of our patients to participate in future research endeavors." *Id.*

Indeed, as the role of personalized medicine and whole-genome sequencing rapidly expands, some geneticists support transparency between researchers and patients as not only a moral and ethical imperative, but also in the best interest of researchers and innovation. Misha Angrist, *You never call, you never write: why return of 'omic' results to research participants is both a good idea and a moral imperative*, 8(6) PMC 651-657 (Dec. 2011).

E. *The Practice of Patenting Human Genes Impinges on Constitutional and Common Law Rights of Privacy and Autonomy*

The Constitutional values of liberty and autonomy require that individuals should be treated as ends in themselves and not merely as means. Furthermore, "our society acknowledges a profound ethical imperative to respect the human body as the physical and temporal expression of the unique human persona." *Moore*, 793 P.2d at 515-16 (Mosk, J. dissenting). The practice of patenting human DNA commodifies human cells *and* the encoded information that guides cellular development. Genetic sequences lay the groundwork for individual identity. It makes little sense to observe a Constitutionally based prohibition on patenting human embryos while allowing a commercial monopoly on segments of an individual's genetic blueprint.

In addition to commodifying human life, patenting human genes impinges on common law and Constitutional rights of privacy. The

Constitutional right of privacy extends to the right to make fundamental decisions that affect self-identity, procreation and the use of one's own body. These privacy interests extend to the right to control one's own DNA. As the Ninth Circuit has observed, "[o]ne can think of few subject areas more personal and more likely to implicate privacy interests than that of one's health or genetic make-up." *Norman-Bloodsaw v. Lawrence Berkeley Lab.*, 135 F.3d 1260 (9th Cir. 1998).

II. RESOLVING THE ISSUE OF WHETHER HUMAN DNA IS PATENT ELIGIBLE SUBJECT MATTER IS CRUCIAL TO MAINTAINING THE PATENT BALANCE BETWEEN REWARDING EXISTING RESEARCH AND ENSURING OPPORTUNITY FOR INNOVATION

As this Court recognized in *Mayo*, the scope of patent-eligible subject matter is not limitless but instead reflects a balance of values. The patent offers a limited monopoly in exchange for information and does so to encourage innovation in the arts and sciences for the public good. The courts have recognized that just as insufficient patent protection fails to incentivize, too much patent protection obstructs the exchange of information necessary for innovation. Hence, for over 150 years, courts have disallowed patent claims that impede future innovation by preempting or broadly covering natural phenomena or natural laws: "The Court has repeatedly emphasized ... a concern that patent law not inhibit further discovery by improperly tying up the future use of laws of nature." *Mayo*, 132 S. Ct. at 1301; *see O'Reilly v. Morse*, 56 U.S. (15 How.) 62, 112-20 (1854) .

In *Mayo*, this Court reaffirmed its prior teaching that patent eligible subject matter under § 101 is limited by exclusions for natural phenomena, laws of nature, and abstract ideas. It reiterated the rationale for these exclusions:

> "Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." And monopolization of those tools through the grant of a patent might tend to impede innovation more than it would tend to promote it.

Mayo, 132 S. Ct. at 1293 (quoting *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)).

With these fundamental concerns in mind, this Court held *Mayo's* patent claims invalid because they effectively do nothing more than describe natural phenomena, *i.e.* correlations governed by natural laws. Steps such as administering an amount of the drug, determining the metabolite concentration, and inferring the need for a change in dosage contributed nothing inventive to the correlations governed by nature that lay at the core of the claimed invention. "[A] process that focuses upon the use of a natural law [must] also contain other elements or a combination of elements, sometimes referred to as an 'inventive concept,' sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself." *Id.* at 1294 (citing *Parker v. Flook*, 437 U.S. 584, 594 (1978)). Focusing on the absence of an "inventive concept," this Court concluded that well-known procedures for administering and determining contributed nothing of ingenuity to the claims.

A. *The Federal Circuit's Majority Decision Wrongly Disregards the Lessons of* Mayo *as Irrelevant to Composition of Matter Claims*

The Federal Circuit majority diminished the applicability of this Court's § 101 jurisprudence by dismissing the relevance of *Mayo* and constructing an arbitrary bright line rule instead of flexible standards provided by this Court. First, this Court remanded this case for further analysis by the Federal Circuit in light of this Court's *Mayo* decision *even though the previous Petition was directed solely to the isolated DNA claims.* Nevertheless, the Federal Circuit dismissed the applicability of *Mayo* to those same isolated DNA claims, holding: "Mayo does not control the question of patent-eligibility of such claims. They are claims to compositions of matter, expressly authorized as suitable patent-eligible subject matter in § 101." *Ass'n for Molecular Pathology v. USPTO*, 689 F.3d 1303, 1325 (Fed. Cir. 2012). In addition, the Federal Circuit majority dismisses the applicability of the *Mayo* decision's principles of preemption because "a composition of matter is not a law of nature." *Id.* at 1331 .

In essence, the Federal Circuit majority determined that the principles and reasoning employed by this Court to analyze subject matter eligibility of process claims are entirely without bearing on or benefit for analyzing subject matter eligibility of composition of matter claims. Using this erroneous logic, the majority simply waved off this Court's admonitions to take guidance from *Mayo*.

B. *The Federal Circuit Majority's Analysis of Patent Eligibility of Human Genetic Sequences is Irreconcilable With This Court's Decisions Governing the Scope of Patentable Subject Matter*

The need for this Court's resolution of whether isolated DNA is patent-eligible is facially apparent from the fact that the four federal judges addressing it employed different analyses. The judiciary needs clarification from this Court. Furthermore, this Court has not addressed the patent eligibility of compositions and manufactures under the judicially created exceptions for natural phenomena since its treatment of this issue in *Diamond v. Chakrabarty*, 447 U.S. 303 (1980) more than 30 years ago. Advances in the life sciences over this period make imperative a further clarification of the application of this exception to § 101.

1. The Federal Circuit's Misapplication of *Funk Bros.* and *Chakrabarty*

The Federal Circuit majority has now twice concluded that Myriad's isolated DNA claims were patentable subject matter by virtue of being "isolated" from their natural environment of the human genome. *Ass'n for Molecular Pathology*, 689 F.3d 1303 (Fed. Cir. 2011) . According to the majority's opinion, isolation requires the breaking of covalent bonds at each end of a gene segment and thereby resulted in a composition having "markedly different characteristics" from the characteristics of the same sequence of nucleotides occurring in the larger genome. *Id.* .at 1328. Although the Federal Circuit relied on the language of *Chakrabarty*, it deviated significantly from the analytic approach taken by *Chakrabarty* and its predecessor, *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948), both of which make clear that function must also be considered.

In *Funk Bros.*, this Court acknowledged that the claimed composition of bacteria was new and useful, but concluded that "[i]t is no more than the discovery of some handiwork of nature and hence is not patentable." *Id.* at 131. Significantly, the Court did not address the structural characteristics of the composition in determining whether it was a product of nature as opposed to a human manufacture. Instead, the Court observed:

> The bacteria perform in their natural way. Their use in combination does not improve in any way their natural functioning. They serve the ends nature originally provided and act quite independently of any effort of the patentee.

Id. Under a similar analysis, this Court in *Chakrabarty* held that patent claims for a genetically enhanced bacterium capable of decomposing oil more effectively was a human manufacture, and therefore fell within subject matter patentable under § 101. In reaching this decision, the Court said nothing about chemical structural differences in explaining how the claimed bacteria were markedly changed. Instead, it differentiated the claimed subject matter by observing that it had a petroleum degrading capability "which is possessed by no naturally occurring bacteria." *Chakrabarty*, 447 U.S. at 305. The analysis in both cases turns on assessing whether the claimed invention describes any performance advantage beyond those inherent in the natural components.

Judge Lourie essentially ignored the "markedly different characteristics" analysis of *Chakrabarty* opting instead to employ a test of "any chemical change" regardless of the claims of the invention. Hence, the majority opinion looks solely for a difference in composition regardless of how small or irrelevant to the properties claimed in the patent. This distortion of "markedly different characteristics" undermines the prior construction of *Chakrabarty* and *Funk Bros.*, which considered structural and functional differences with natural phenomena.

If *Funk Bros.* and *Chakrabarty* guide away from a narrow concern with structural chemical differences in assessing patent eligibility of biological technology, *Mayo* reinforces the view that changes incidental to the isolation and purification of natural material do not render it patentable.

2. The Proper Application of *Mayo*

In *Mayo*, this Court questioned whether: "the patent claims add *enough* to their statements of the correlations to allow the processes they describe to qualify as patent-eligible processes that *apply* natural laws?" *Mayo*, 132 S. Ct. at 1297. The correlative question in this case is whether the process of isolating DNA and the attendant changes that occur at the terminal ends of an isolated gene make it different *enough* to *transform* it in any defining way. Based on this Court's reasoning in *Funk Bros.*, *Chakrabarty*, and now *Mayo*, the answer is no. Isolating a natural substance is not an inventive step. As the Federal Circuit recognized in *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293 (Fed. Cir.

2007), "isolation of interesting compounds is a mainstay of the chemist's art," and that "[i]f it is known how to perform such an isolation doing so 'is likely the product not of innovation but of ordinary skill and common sense.'" *Id.* at 1302 (citing *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)). Secondly, the structural change that occurs as a consequence of isolation—breaking covalent bonds—has no bearing on what DNA is or does. Such changes do not alter the claimed or defining *properties* of DNA. It is not *enough* to identify slight molecular differences in the ends of a complex polymer chain if such differences bear no relationship to any change in the properties claimed or any inventive concept or solution to a problem.

In this case, the patent claims describe a sequence of nucleotides or amino acids without regard to miniscule differences in molecular characteristics of terminal points. The patents at issue do not teach the importance or value of the terminal ends of the isolated DNA. In fact, the importance associated with the terminal ends of the composition relied on by the Federal Circuit majority is undermined by the claims to "at least 15 nucleotides" that cover numerous compositions with different terminal ends. For example, claim 6 of the Patent No. 5,747,282 for "an isolated DNA having at least 15 nucleotides of the [nucleotide sequence set forth in SEQ ID NO:1]" covers over 17 million compositions at least 15 nucleotides long within the 5,914 nucleotide sequence.[5] Such differences at the terminal ends are irrelevant to the structure of the nucleotide sequence or coding function that defines DNA.

3. Isolation Does Not Transform a Genetic Sequence Into a Human Manufacture

The fact that a segment of DNA—the encoding sequence—is obtained through human initiative does not transform what is natural and inherent in the sequence of nucleotides or bring about any new capabilities. Regardless of the human ingenuity and labor required to isolate, extract or purify a segment of human DNA, the sequence of nucleotides remain a product of nature. As stated by this Court over a century ago:

> There are many things well known and valuable in medicine or in the arts which may be extracted from...substances. But the extract is the same, no matter from what it has been taken. A process to obtain it from a subject from which it has never been taken may be the creature of invention, but the thing itself when

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[5] The 17 million compositions would not include the claimed compositions having at least 15 nucleotides of SEQ ID NO:1 but not found within the 5,914 nucleotides listed in SEQ ID NO:1.

> obtained cannot be called a new manufacture.

American Wood-Paper Co. v. Fibre Disintegrating Co., 90 U.S. (23 Wall.) 566, 593-94 (1874) .[6]

III. MYRIAD'S CLAIM FOR "COMPARING" CELL GROWTH RATES IS DIRECTED TO PATENT INELIGIBLE NATURAL LAWS

The district court held claim 20 of the '282 Patent invalid because it is directed to the abstract mental processes of the scientific method itself.

On an initial review the Federal Circuit reversed the district court, finding Claim 20 patent eligible. Subsequently, this Court vacated the Federal Circuit's opinion in light of this Court's decision in *Mayo* and remanded the case. Following this Court's remand in light of *Mayo*, the Federal Circuit again found claim 20 of the '282 Patent valid based upon the use of "transformed cells." The reliance solely upon "transformed cells" to find patent eligibility ignores the analysis and application of this Court's decision in *Mayo*.

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[6] *See also Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293 (1884) (finding artificial alizarine derived from a precursor substance and having the same properties as those found in natural alizarine was not patentable); *Ex parte Latimer*, 1889 Dec. Comm'r Pat. 123 (finding purified pine needle fiber not patentable).

A. *Using "Transformed Cells" Does Not Render a Method Patent-Eligible Under* Mayo

Without citing any authority, the Federal Circuit majority asserts that "once one has determined that a claimed composition of matter is patent-eligible subject matter, applying various known types of procedures to it is not merely applying conventional steps to a law of nature." *Ass'n for Molecular Pathology*, 689 F.3d at 1336. Based upon this reasoning, the Federal Circuit incorrectly found the use of transformed eukaryotic cells sufficient to make the entire method claim patent eligible without regard to the claimed steps.

The basis for this conclusion is flawed in light of *Mayo* because the method in *Mayo* used "thiopurine drugs" that are likely patent eligible under § 101,[7] yet the method of testing their proper dosage remained patent ineligible. *Mayo* did not consider the potential patent eligibility of *a product* used in the method sufficient to render the method itself eligible.[8] Based upon *Mayo*, a method claim limited to the use of conventional and routine steps applied to a natural law is not rendered patent-eligible under § 101 by the mere inclusion of a potentially patent-eligible product used in the process.

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[7] They would be likely be unpatentable under §§ 102 and 103 based upon prior art.

[8] Ironically, despite dismissing the relevance of *Mayo* to products of nature, the Federal Circuit's analysis reduces the patent eligibility of a process claim to the question of whether one of the compositions used is not a product of nature.

Moreover, the mere inclusion of a potentially patent eligible product within a process would not constitute "an 'inventive concept,' sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself" as required by *Mayo*. *Mayo*, 132 S. Ct. at 1294 (citing *Parker v. Flook*, 437 U.S. 584, 594 (1978)).

B. *The Claimed Steps Add Nothing of Significance to the Natural Laws*

Claim 20 is directed to three main steps: (1) growing two transformed eukaryotic host cells with altered BRCA1 genes, one in the presence of a compound and one in the absence of the compound; (2) determining the rates of growth for each of the host cells; and (3) comparing the growth rates of the host cells. The claim further indicates that "a slower rate of growth of the host cell in the presence of the compound is indicative of a cancer therapeutic."

The growing step (1) is analogous to the "administering" step of the Prometheus claims—a step that simply told doctors to provide thiopurine drugs to patients as they had previously. *Mayo*, 132 S. Ct. at 1297. In the present case, the growing steps do no more than direct a scientist to grow eukaryotic host cells, a process that was known and routinely performed. *See* '282 Patent Col. 27 Lns.

41-52 (acknowledging that "propagation of mammalian cells [which are a type of eukaryotic host cells] in culture is per se well known."). In both cases, this claimed routine and conventional step included the utilization of a potentially patent-eligible product—*i.e.* thiopurine drugs in *Mayo* and a transformed eukaryotic cell in the present case.

Similarly, the determining step (2) is equivalent to the "determining" step in *Mayo*. In *Mayo*, the "determining" step told the doctor to determine the level of metabolites "through whatever process the doctor or the laboratory wishes to use." *Mayo*, 132 S. Ct. at 1297. In the present case, the '282 Patent does not explain the process beyond stating that "the rate of growth of the host cells is measured," indicating that methods of measuring the rate of growth would be known in the art. *See* '282 Patent Col. 31 Lns. 46-53. Accordingly, these steps instruct the scientists to perform conventional activity to measure growth rates of cells in each environment (*i.e.* the presence or absence of the compound).

The final comparing step instructs the scientists to look at the results of each growth rate measurement. This step is equivalent to comparing metabolite levels with those required by the Prometheus claims. A comparison of results is a conventional and routine aspect of scientific testing that is exemplified by the scientific method.

Finally, the wherein clauses in both the Prometheus claims and Myriad's '282 Patent claim identify relevant natural laws. In this case, the natural law provided in the wherein clause is the natural correlation between a slower growth rate in the presence of a compound indicating a potential cancer therapeutic.

C. *Application of the Scientific Method to a Natural Phenomena is an Abstract Process*

Claim 20 is nothing other than the application of scientific method to evaluate natural effects of compounds on the growth rate of host cells. In simple terms, this is a test wherein you (1) prepare a test sample having the hypothesized element (*i.e.*, the compound) and a control sample without the hypothesized element; (2) allow a reactionary process to occur; (3) observe the results of both samples; and (4) draw a conclusion related to the original hypothesis (*i.e.*, whether the compound is indicative of a cancer therapeutic). Applying the scientific method using routine and/or conventional steps does not add any significance to the natural laws and does not make them patentable applications.

CONCLUSION

As the history and diversity of judicial opinions in this case reveal, federal courts need guidance so they can distinguish between products that are predominantly, if not entirely, the work of nature (and therefore ineligible for patent protection) from those that are sufficiently changed by virtue of human ingenuity to qualify as patent eligible subject matter under § 101. This case, more than any other, illustrates why the building blocks of human knowledge, including the human genome, should not be subject to monopoly through patent law. Extending patent protection to human genes results in less, not more, innovation in a sphere of research activity where innovation and freedom from monopoly are vital to the prevention and treatment of life threatening diseases. For the reasons herein, Amici respectfully request that this Court accept this case for review.

Respectfully submitted,

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October 31, 2012

AMICUS
CURIAE
BRIEF

Supreme Court, U.S.
FILED
OCT 30 2012
OFFICE OF THE CLERK

No. 12–398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, THE AMERICAN COLLEGE OF MEDICAL GENETICS, THE AMERICAN SOCIETY FOR CLINICAL PATHOLOGY, THE COLLEGE OF AMERICAN PATHOLOGISTS, HAIG KAZAZIAN, MD, ARUPA GANGULY, PHD, WENDY CHUNG, MD, PHD, HARRY OSTRER, MD, DAVID LEDBETTER, PHD, STEPHEN WARREN, PHD, ELLEN MATLOFF, MS, ELSA REICH, MS, BREAST CANCER ACTION, BOSTON WOMEN'S HEALTH BOOK COLLECTIVE, LISBETH CERIANI, RUNI LIMARY, GENAE GIRARD, PATRICE FORTUNE, VICKY THOMASON, and KATHLEEN RAKER,

Petitioners,

v.

UNITED STATES PATENT AND TRADEMARK OFFICE
and
MYRIAD GENETICS, INC.,

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF *AMICI CURIAE* CANCER COUNCIL AUSTRALIA, THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA, HUMAN GENETIC SOCIETY OF AUSTRALASIA, NATIONAL BREAST CANCER FOUNDATION, and LUIGI PALOMBI PHD IN SUPPORT OF PETITIONER

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STATEMENT OF INTEREST[*]

Cancer Council Australia is Australia's peak national non-government cancer control organization. It advises the Australian government and other Australian non-government bodies on practices and policies to help prevent, detect and treat cancer. It also advocates for the rights of cancer patients for best treatment and supportive care. It works with its members, the eight Australian state and territory cancer organizations, to undertake and fund cancer research, prevent and control cancer and provide information and support for people affected by cancer.

The Royal College of Pathologists of Australasia, established in 1956, is the leading organization representing pathologists in Australasia. In 1970 Her Majesty, Elizabeth II, assented to the inclusion of "Royal" in the title. Its mission is to train and support pathologists and to improve the use of pathology testing to achieve better healthcare and is responsible for the promotion of the science and practice of pathology in the Australasian region. Pathology is about the study of the causes of disease, and pathologists are the specialist medical doctors involved in the diagnosis and monitoring almost of all acute and chronic illnesses. It publishes the quarterly scientific journal *Pathology*. Members come from across Australasia including Australia, New Zealand, Hong Kong, Singapore, Malaysia and Saudi Arabia.

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[*] No party or counsel for a party authored or contributed monetarily to the preparation or submission of any portion of this brief. Counsel of record for all parties received notice of Amici's intention to file this brief more than 10 days before it was due. Petitioner has filed with the Clerk of the Court a letter granting blanket consent to the filing of *amicus* briefs, and a letter reflecting the consent of respondent to the filing of this brief has been filed with the Clerk.

The Human Genetics Society of Australasia was formed in 1977 to provide a forum for the various disciplines collected under the title of Human Genetics in the Australasian region. Membership consists of ordinary members who are defined as those who hold a recognized qualification in a discipline relevant to Human Genetics and are employed in a position appropriate to this discipline, whether it be as a teacher, clinician, laboratory scientist, counselor or in pure research. Membership includes those who reside outside Australia, students, organizations and associate memberships. Emeritus membership is achieved by invitation only, in recognition of eminence in the field.

The National Breast Cancer Foundation, established in 1994, is Australia's leading community-funded national organization dedicated to the support, promotion and funding of research into the prevention and cure of breast cancer. It has, to date, been responsible for awarding nearly 300 research projects valued at over $81 million. It is widely recognized by the Australian people, Australian corporations, Australian State and Federal governments and Australian researchers for the charitable services it provides in supporting those affected by breast cancer including their families.

Luigi Palombi, PhD, is a lawyer. He has, since 1993, specialized in the field of biotechnology and gene patents. (*See*: *The Patenting of Biological Materials in the Context of TRIPS*, PhD thesis, The University of New South Wales (2004); *Gene*

Cartels Biotech Patents in the Age of Free Trade (Cheltenham U.K. and Northhampton U.S.A.: Edward Elgar (2009)).

SUMMARY OF ARGUMENT

The most fundamental principle of patent law is the social contract between an inventor and the State. At the heart of a patent is an invention. For the purposes of Anglo-American patent law this principle was codified in England in the Statute of Monopolies of 1623.[1] Revoking "all monopolies" as being "utterly void and of none effect", one of the few exceptions made to this prohibition was for letters patent not exceeding 14 years granted to the "true and first inventor" of "any manner of new manufacture".[2]

This principle was adopted in the U.S. Patents Act, 1790 and continues to be part of U.S. patent law. *Mayo Collaborative Servs v. Prometheus Labs., Inc.*, 132 S. Ct 1289 (2012) (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980)). As a result, "laws of nature, natural phenomenon, and abstract ideas" are not patentable subject matter.

The application of this principle in a line of U.S. Supreme Court authority starting with *O'Reilly v. Morse* 56 U.S. (How.) 62 (1853) has not, however, resolved the current controversy which has raged for 30 years. Nowhere is this more apparent than on the facts of this case. As to what is a "composition of matter" within 35 U.S.C. § 101 (and therefore patentable subject matter) as distinct from a "natural phenomenon" (and therefore not patentable subject matter), the definitive ruling in *Diamond v. Chakrabarty* ("a new bacterium with *markedly different characteristics from any found in nature* and one having the potential for significant utility" is patentable subject matter). (Id., at 310) has been misapplied by USPTO.

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[1] The common law first applies this policy in *Darcy v Allein (The Case of Monopolies)* (1602) 77 ER 1260.

[2] Section 6, Statute of Monopolies, 1623.

In summary, the first of three issues, which has arisen since *Diamond v. Chakrabarty* and which is raised for the first time in U.S. jurisprudence by this case, is whether a biological material, such as a DNA molecule, that has been isolated, in other words, removed from its natural environment but which is otherwise identical, is a "composition of matter" within 35 U.S.C. § 101. That this issue was not reached in *Diamond v. Chakrabarty* is long acknowledged. *See* Rebecca S. Eisenberg, *Proprietary Rights and the Norms of Science in Biotechnology Research*, 97 YALE L. J. 177, 189 (1987), BRIEF FOR THE UNITED STATES AS AMICUS CURIAE IN SUPPORT OF NEITHER PARTY, 6 (*Association for Molecular Pathology v. United States Patent & Trademark Office and Myriad Genetics, Inc.* (Fed. Cir.)) and *Intervet, Inc v. Merial Ltd.*, 617 F.3d 1282, 1293 (Fed. Cir. 2010) (Dyk, J., concurring in part) (observing that "thus far the question as evaded judicial review").

The second issue to arise is the extent to which an artificial construct of a biological material, such as a complementary DNA molecule (cDNA) capable of performing the identical function of the natural DNA molecule, that is, encoding a protein that is identical or substantially identical to the protein encoded by the natural DNA molecule, is a "composition of matter" within 35 U.S.C. § 101. The patent claims in issue are directed to cDNA molecules containing the same, or effectively the same, genetic information encoding naturally occurring human proteins BRCA 1 and BRCA 2, specifically to characteristics, which have been linked to breast and ovarian cancers. The issue, therefore, is the degree of artificiality required to be transformative. Is it enough that the cDNA molecule is man-made?

Finally, the Court in *Diamond v. Chakrabarty* referred to the "gruesome parade of horribles", a list of negative consequences put up by the U.S. government and other amici, that would befall society should the patenting of genetically modified life forms be allowed (Id., at 316), but ruled it was "without competence to entertain [them] – either to brush them aside as fantasies generated by fear of the unknown, or act on them". (Id, at 317). It, instead, relegated the task of balancing the "competing values and interests" exclusively to the "elected representatives" (Id., at 317) for the reason that its task was "the narrow one of determining what Congress meant by the words it used in the statute; once that is done our powers are exhausted." (Id., at 318). That said, there is 150 years of U.S. Supreme Court authority ("The laws of nature, physical phenomena, and abstract ideas have been held not patentable.") which falls fairly and squarely within U.S. Const., Art I, §8, cl. 8.

To be sure, if this narrow approach be correct then it applies equally to both sides of the argument in this case. Accordingly, whatever "gruesome parade of horribles" the patentee and its supporters may predict, they are irrelevant. Nonetheless, there is reason to question the correctness of this approach.

The resolution, by this Court, of these three issues is of great importance to the development of patent law beyond the United States. The Australian patent system shares common roots with the U.S. patent system. It too upholds the fundamental principle of invention and excludes products of nature from patentability. Like the United States there is a need for jurisprudential input on the issues raised by this case. And while the Australian courts are at liberty to come to their own conclusions on Australian patent law, the High Court of Australia is increasingly looking to the jurisprudence of U.S. courts for guidance on patent related issues. ("The reasoning in ... United States authorities should be accepted in preference to the path apparently taken in the English decisions, ... The United States decisions reflect an approach to the subject closer to that adopted in *Minnesota Mining* and *Wellcome Foundation*." *Aktiebolaget Hässle v. Alphapharm*. (2002) 212 CLR 411). Presently, there is no Australian court decision on the issues raised in this case. Therefore, in the circumstances, the intersession of this august Court is vital, not only to resolving this longstanding controversy in the United States, but in providing input into the development of societal opinions and patent law in Australia.

ARGUMENT

A. The Social Contract is of Paramount Importance to the Legitimacy of the Patent System.

Whatever the rationale for the creation of statutory monopolies, the social contract is of utmost importance to the legitimacy of the U.S. patent system - indeed, for all patent systems. (*See* Adam Mossoff, *Who Cares What Thomas Jefferson Thought About Patents? Reevaluating the Patent "Privilege" in Historical Context*, 92 CORNELL L. REV. 953 (2007)). It is the social contract between the inventor and the State that links the U.S. patent system to all other patent systems. And it is the most fundamental principle of patent law that without an 'invention' the grant of a patent is void *ab initio*. That a patent is today property, not a privilege, makes no difference to the application of that principle. A patent can be revoked if the consideration for the social contract, the invention, is found wanting. (*SmithKline Beecham v. Apotex* 403 F 3d 1346 (Fed. Cir., 2006). (Gajarsa J., observing: "Both this court and the Supreme Court have recognized that there is a significant public policy interest in removing invalid patents from the public arena", Id., at 1354).

As to what can be the proper subject of a patent, 35 U.S.C. § 101 lays down the statutory requirements under U.S. patent law. As a result, "laws of nature, natural phenomenon, and abstract ideas" are not patentable subject matter. (*Mayo Collaborative Servs v. Prometheus Labs., Inc*, quoting *Diamond v. Chakrabarty*). Anything which falls within the boundaries of this principle is incapable of being the subject of the grant of a valid patent.

Thus the distinction between "composition of matter" and "natural phenomena" must be both comprehensible and strictly applied if the principle, most recently restated by this Court in *Mayo Collaborative Servs v. Prometheus Labs., Inc,* is to have any practical purpose in the 21st century. ("*[T]oo much* patent protection can impede rather than "promote the Progress of Science and useful Arts," the constitutional objective of patent and copyright protection. U.S. Const., Art I, §8, cl. 8". Justices Breyer, Souter and Stevens (in dissent on the dismissal of the grant of certiorari) *Labcorp v. Metabolite Laboratories, Inc.* 126 S. Ct 2921 (2006)).

This case highlights the importance of this distinction in the context of the social contract. The subject matter in issue are 'isolated' DNAs and cDNAs, which encode proteins linked to breast and ovarian cancers in humans. Neither the isolated DNAs nor the proteins for which they code, except for the fact that the DNAs are isolated from their natural environments, are different in any material way to what they are and how they function in a human body. They are natural phenomena in every sense of the term. That cDNAs are little more than copies of their natural corresponding counterparts also makes them natural phenomena even though they are artificial. For the first time since USPTO first granted such patents this Court has the opportunity to consider and rule on this most important issue; an issue that unless resolved threatens to undermine the legitimacy of the U.S. patent system, indeed, the legitimacy of other patent systems which have misguidedly followed USPTO policy.

B. The Isolation Contrivance and the Isolation of DNAs and cDNAs.

Naturally occurring biological materials in an isolated or purified form are the same in terms of what they are and what they do except for one thing; they are no longer in their natural environments. This fact is acknowledged in the patents in issue. Taking U.S. Patent 5,747,282 as an example, the definition of 'isolated' or 'substantially pure' is:

> An "isolated" or "substantially pure" nucleic acid (e.g. an RNA. DNA or a mixed polymer) is one which is substantially separated from other cellular components which naturally accompany a native human sequence or protein. e.g., ribosomes, polymerases, many other human genome sequences and proteins. The term embraces a nucleic acid sequence or protein which has been removed from its naturally occurring environment. And includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems.

The interchangeability of the word 'isolated' by the term 'substantially pure' in this definition is significant. According to the patent there is no *material point* of physical distinction between something that is 'isolated' from something that is 'substantially pure'. Consequently, an 'isolated' DNA molecule or a 'substantially pure' protein is, by definition, either identical or substantially identical in structure and function to the respective DNA molecule or protein in its natural environment. In other words, the isolation/purification of the relevant DNAs and the proteins for which they code is a form of legal semantics that cannot legitimately differentiate, as a 'fact', one biological material from another. Thus explained the distinction, which the word 'isolation' or the term' substantially pure' imply, is but a contrivance - "the isolation contrivance". The change in physicality is *in situ* not *in substance*. (See Luigi Palombi, *Gene Cartels*, supra, 205-225).

Also notable is the inclusiveness in the definition of "native human sequences" on the one hand and "proteins" on the other. Triplets of DNA, known as "codons" (e.g., GTG, AAG, etc. etc.,) code for a single amino acid (there are 20 naturally occurring amino acids which are the chemical building blocks of proteins). Though related, they are very different in structure and function. DNA is informational (genetic sequence), whereas the protein (amino acids) encoded by that DNA is the physical manifestation of that information. DNA and the encoded protein are inextricably linked much like the digital information recorded on a DVD is linked to the sound and picture ultimately produced when the DVD is played.

Critically, a change in the DNA sequence produces a change in the three dimensional shape, or structure, of a protein and it is for this reason, particularly true when a diagnostic or therapeutic application of a naturally occurring protein in a human is envisioned, that both the DNA sequence of the DNA molecule and the amino acid sequence of the protein must correspond identically or substantially so, regardless of whether they are isolated or purified or not, to these materials as they exist in nature.

Returning to the '282 patent, the definition of "BRCA1 Locus", "BRCA1 Gene" and "BRCA1 Nucleic Acids" or "BRCA1 Polynucleotide" links them to:

> a sequence which is either derived from or substantially similar to a natural BRCA1-encoding gene or one having substantial homology with a natural BRCA1-encoding gene or a portion thereof. The coding sequence for a BRCA1 polypeptide is shown in SEQ ID NO:1. with the amino acid sequence shown in SEQ ID N0:2.

Turning specifically to claim 1 of the '282 patent, the invention is defined as follows:

> 1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID N0:2.

In simple terms, the subject matter of the patent as defined in claim 1 is a biological material in an isolated form, but, which is in every other way identical to what exists in nature. Indeed, the accuracy and reliability of a diagnostic test using this material to produce a clinically significant result is dependent upon that *exact* identity.

The logical law of identity is one of the three foundational laws of logic identified by Aristotle, and accepted as an axiom in the sciences even today. Simply put, the law states: A=A. (*See*: Irving M. Copi and Carl Cohen, *Introduction to Logic, 11th Edition* (USA: Prentice Hall) (2001)). The isolation contrivance, however, violates the law of identity. Logically, it suggests that Joseph Priestley would have been entitled to a patent on oxygen given his discovery of a new *process* for liberating and isolating oxygen from mercuric oxide. This 'isolation' of a naturally-occurring molecule, otherwise morphologically identical to oxygen in other forms, would arguably produce a patent-eligible *product* under Section 101. But it defies logic and is precisely analogous to the present dispute about the patented BRCA1 and 2 genes. It also illustrates the absurd implications of the isolation contrivance.

As explained above, the patented *product* encompasses a product that is morphologically identical to the naturally-occurring BRCA1 and 2 genes, (*See*: David Koepsell, *Who Owns You? The Corporate Gold Rush to Patent Your Genes*, (UK: Blackwell-Wylie) (2009), p. 6) just as Dr. Priestley's oxygen is identical to the oxygen produced naturally by photosynthesis. In essence, under modern patent law, isolation contrivance says that A does not equal A, or oxygen does not equal oxygen, or BRCA1 and 2 do not equal BRCA1 and 2. The law ought to be consistent at the very least with the fundamental laws of thought, rules of logic that make argumentation both possible and useful, and axioms that underlie all the sciences. By perpetuating this notion, that somehow identical biological materials are not identical because one is isolated and the other is not, is not only strained, but illogical.

C. "Everything Under the Sun Made By Man".[3]

Historically the U.S. Supreme Court has invalidated patents on the grounds that they are "products of nature". (*American Wood Paper v. Fibre Disintegrating*, 90 U.S. 566 (1874); *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293 (1884); *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948)).

The eligibility of patenting products of nature arose in *General Electric Co. v. De Forest Radio Co.* 28 F.2d 641 (3rd Cir., 1928). ("[A] patent cannot be awarded for a discovery or for a product of nature, or for a chemical."). (Id., at 642). Dr. William D. Coolidge, the inventor, referred to his material as a new metal, a pure tungsten and he applied for a patent. His process consisted of converting WO_3 (tungsten III oxide) into pure tungsten. First, WO_3 is heated in a gas furnace in order to liberate oxygen, carbon, and chemical impurities. The resulting product was then heated electrically changing the substance from the yellow oxide to the blue oxide to the bronze oxide and then finally to pure tungsten. These various oxides of tungsten are different, with distinct properties from pure tungsten. However, the court denied his patents on the so-called pure tungsten. ("[W]ho created the pure tungsten. Coolidge? No. It existed in nature and doubtless has existed there for centuries. The fact that no one before Coolidge found it there does not negative its origin or its existence."). (Id., at 643). Similarly, genes have existed in nature for centuries and the fact that the patentee linked naturally occurring DNA to naturally occurring proteins that are causative of breast and ovarian cancers does not negate their origin.

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[3] ["Under] section 101 a person may have invented *a machine or a manufacture*, which may include anything under the sun that is made by man. ...". (Hearings on H. R. 3760 before Subcommittee No. 3 of the House Committee on the Judiciary, 82d Cong., 1st Sess., 37 (1951). (Emphasis added)

The Court also questioned whether the properties of the tungsten produced by the Coolidge process (ductility and a high tensile strength) could be attributed to Dr. Coolidge. ("Did Coolidge give those qualities to 'substantially pure tungsten'? We think not for it is now conceded that tungsten pure is ductile cold. If it possesses that quality now, it is certain that it possessed it always."). (Id., at 643). Similarly, the sequence of the gene, the sequence of variants, and the significance of the variants have always been there and their characteristics, to use the language of Court in *Diamond v. Chakrabarty,* cannot be attributed to their isolation or purification.

Mr. Pascquale J. Federico, referred to in a footnote in the *Diamond v Chakrabarty* decision, had been an employee of the USPTO for 5 years when *General Electric Co. v. De Forest Radio Co.* was handed down. Having risen through the ranks of the USPTO to Division Chief in 1940 and appointed to the Board of Patent Appeals in 1947, in 1950 he was assigned the task of drafting what became the Patents Bill in 1951. And it was during testimony to a Congressional review of the Patents Bill that he made one of the most often cited statements in modern patent law and one cited with approval by the Court in *Diamond v Chakrabarty*, namely: ["Under] section 101 a person may have invented a machine or a manufacture, which may include anything under the sun that is made by man. ...". (Hearings on H. R. 3760 before Subcommittee No. 3 of the House Committee on the Judiciary, 82d Cong., 1st Sess., 37 (1951), referred to in *Diamond v Chakrabarty*, footnote 6 at 309).

Even so the Court qualified Mr. Federico's words in the context of 35 U.S.C. § 101 by reinforcing the fundamental principle that "laws of nature, physical phenomena, and abstract ideas" remain outside of the "broad language" used to define "statutory subject matter". The genetically modified bacterium in issue in that case was ruled to be patentable subject matter *only* because it displayed "markedly different characteristics from any found in nature". And while the Court also found that "the respondent's micro-organism is the result of human ingenuity and research", it was not decisive. Accordingly, artificiality per se is not sufficiently transformative of a natural biological material. Much more is required.

However, USPTO misapplied *Diamond v. Chakrabarty* by relying on Mr. Federico's words as if they are, by themselves, an accurate restatement of statutory subject matter. Compounding the problem and providing some, albeit erroneous, justification for its policy is *Parke-Davis & Co. v. H. K. Mulford Co.* (189 F. 95, 1911), which concerns a patent granted over purified adrenalin. It is often cited by proponents of the patenting of isolated DNAs and cDNAs, yet the Federal Circuit distinguishes it on its facts. (per Lourie J., "*Parke-*

Davis and *Marden* address a situation in which claimed compound A is purified from a physical mixture that contains compound A. In this case, the claimed isolated DNA molecules do not exist as in nature within a physical mixture to be purified").

Recognizing the problem with *Parke-Davis & Co.* the Federal Circuit attempts to apply the distinction between a "product of nature" and a "human-made invention" on the basis that the isolated DNAs in issue are, "chemically cleaved from their native chemical combination with other genetic materials [and] ... when cleaved, an isolated DNA molecule is not a purified form of a natural material, but a distinct chemical entity that is obtained by human intervention." (per Lourie J.) Apart from the fact that neither the patentee in submission nor in evidence made this point, the patent itself makes no such distinction and defines the term "isolated" by reference to both DNAs and proteins having been "substantially separated from other cellular components which naturally accompany a native human sequence or protein." It also expressly defines the term "isolated" to mean the same as "substantially pure". ("The term embraces a nucleic acid or protein which has been removed from its naturally occurring environment ..."). ('828 at 19, lines 13-15). The patent's very language therefore undermines the Federal Circuit's reasoning, which brings *Parke-Davis & Co.* back into contention. (For a critique of the reasoning in *Parke-Davis & Co: See* Jon M. Harkness, *Dicta on Adrenalin(e): Myriad Problems with Learned Hand's Product-of-Nature Pronouncements in Parke Davis v Mulford,* 93(4), J. PAT. OFF. SOC., (2011)). The same concerns arise with regard to cDNAs.

In other words, was the patented bacterium in *Diamond v. Chakrabarty* "new" merely because it was artificial? If it was, then how is it reconciled with *Cochrane v Badische Anilin & Soda Fabrik* 111 U.S. 293 (1884)? ("Calling it artificial alizarine did not make it a new composition of matter, and patentable as such, by reason of its having been prepared artificially for the first time from anthracene, if it was set forth as alizarine, a well known substance."). (Id., at 311). The answer to this question is also of relevance in view of *Ex parte Latimer,* 1889 Dec. Com. Pat. 123 in which the Commissioner of Patents rejected a claim to a naturally occurring biological material, a fiber derived from the needle of a species of pine tree, even though it was in an 'isolated' form. ("[P]atents [to] be obtained upon the trees of the forest and the plants of the earth, which of course would be unreasonable and impossible."). (Id., at 126). The patenting of new varieties and cultivars of plants is noteworthy since the relevant policy issues concerning their patenting were only resolved by specific legislation. (*See* Plant Patent Act, 1930 and the Plant Variety Protection Act, 1970). To be sure, in passing the Plant Patent Act, Congress "recognized the relevant distinction was not between living and inanimate things, but between products of nature, whether living or not, and human-made inventions" (*Diamond v. Chakrabarty,* 447 U.S. 303, 313), but even so, how much "human ingenuity and research" (Id., at 313) is required before an artificial product derived from a naturally occurring biological material, such as the cDNA molecules at issue in this case, is patentable subject matter?

D. The U.S. Supreme Court's Role in Regard to Patent Policy.

The Court in *Diamond v. Chakrabarty* ruled that the task of balancing the "competing values and interests" over the patenting of life forms was a matter exclusively for the "elected representatives". (Id., at 317). It also narrowly construed the role of this Court: ([Its task is] "the narrow one of determining what Congress meant by the words it used in the statute; once that is done our powers are exhausted." (Id., at 318). That said, there is 150 years of U.S. Supreme Court authority ("The laws of nature, physical phenomena, and abstract ideas have been held not patentable.") which falls fairly and squarely within U.S. Const., Art I, §8, cl. 8.

Nonetheless, there is reason to question this Court's narrow approach in *Diamond v. Chakrabarty* in the formulation of patent policy. Indeed, one need only look to the role the courts played in the 19th century, in transforming patents from a privilege into a property right, to realize how they have shaped modern patent law. (*See* Adam Mossoff, *Who Cares What Thomas Jefferson Thought About Patents? Reevaluating the Patent "Privilege" in Historical Context*, 92 CORNELL L. REV. 953 (2007)). At what point does this august Court abrogate its responsibility to society? ("*[T]oo much* patent protection can impede rather than "promote the Progress of Science and useful Arts," the constitutional objective of patent and copyright protection. U.S. Const., Art I, §8, cl. 8". (per Justices Breyer, Souter and Stevens in dissent in *Labcorp v. Metabolite Laborato-*

ries, Inc. 126 S. Ct 2921 (2006)).

Respectfully, if statutory interpretation be this Court's only role then it must, for two reasons, reconsider the reliance placed by the Court in *Diamond v. Chakrabarty* on the Congressional testimony of Mr. P. J. Federico. ("[Under] section 101 a person may have invented a machine or a manufacture, which may include anything under the sun that is made by man. ..." Hearings on H. R. 3760 before Subcommittee No. 3 of the House Committee on the Judiciary, 82d Cong., 1st Sess., 37 (1951). (Id., at 309)).

First, Mr. Federico was greatly influenced by Judge Learned Hand's decision in *Parke-Davis & Co.* (*See* P. J. Federico, *Patents For New Chemical Compounds*, 21(7) J. PAT. OFF. SOC., 544, (1939), 549, fn 9). The problem, however, is that patentable subject matter was not in issue in that case. Accordingly, Judge Hand's comments were strictly *obiter dicta* ("... even if it were merely an extracted product without change, there is no rule that such products are not patentable subject matter."; Id., at 103). Understandably, Judge Hand did not address *Ex parte Latimer* 1889 Dec. Com. Pat. 123. (*See* Jon M. Harkness, *Dicta on Adrenalin(e): Myriad Problems with Learned Hand's Product-of-Nature Pronouncements in Parke Davis v Mulford,* 93(4), J. PAT. OFF. SOC., (2011), Lori B. Andrews, *Genes and Patent Policy: Rethinking Intellectual Property Rights,* 3 NAT. REVS: GENETICS, 803 (2002), and J. Doll, *The Patenting of DNA,* 280 SCIENCE, 689 (1998)).

Secondly, in 1939 Mr. Federico posed this question: "[i]f a substance, hitherto not known to exist, is discovered in some plant or animal material, extracted in concentrated or pure form, and demonstrated to be highly useful, can the product be patented?". (Id, at 549). To which he replied: "A categorical answer of 'No, because the substance is not really new,' cannot be made". (Id., at 549). This answer, given some 14 years before Drs. James Watson and Francis Crick discovered the molecular structure of DNA reveals, even with the benefit of hindsight, a rudimentary understanding of the biological sciences and an idiosyncratic approach to what is 'new'. (Id., at 549).

It is arguable, on the basis of this perspective, that in 1951 Mr. Federico's opinion that "anything under the sun made by man" was patentable subject matter was erroneous. Artificiality *per se* was neither then, nor has it since been, the sole indicium of patentable subject matter. In fact, apart from *Parke-Davis & Co.* there was no authority in 1951 for such a proposition in law. More to the point, the Court in *Diamond v. Chakrabarty* has since unequivocally stipulated that artificiality *per se* is not enough ("markedly different characteristics from any found in nature", Id., at 310). Whatever remaining argument, no matter how flawed it might be, over how to draw the line between "composition of matter" and "natural phenomena" must be erased once and for all.[4]

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[4] Mr. Federico conceded that the patent claim granted to Louis Pasteur (U.S. Patent No. 135,245 granted January 28, 1873: "Yeast, free from organic germs, as an article of manufacture.") would have "probably been refused by [an] examiner" in light of *American Fruit Growers v. Brogdex* 283 U.S. 1 (1931). (See P.J. Federico, *Louis Pasteur's Patents*, 86 SCIENCE, 327 (1937).

E. Clarification is a Matter of Great Importance to Health Policy and National Security.

The need for clarification with respect to these issues is not only of "great importance to the national economy, to medical science, and to the public health". (*See* BRIEF FOR THE UNITED STATES AS AMICUS CURIAE IN SUPPORT OF NEITHER PARTY, 6 (*Association for Molecular Pathology v. United States Patent & Trademark Office and Myriad Genetics, Inc.* (Fed. Cir., 2010)). It is also of great importance to the national security of the United States for the reason that should the threshold of patentability be set too low, the U.S. patent system may be used, much like it was used by German chemical companies prior to WWI, to suppress chemical research and industry within the United States, to suppress medical and scientific research and industry in the future. (*See* Floyd W. Vaughan, *Suppression and Non-Working of Patents, With Special Reference to the Dye and Chemical Industries*, 9 AMER. ECO. REV., 693 (1919); Kathryn Steen, *Patents, Patriotism, and "Skilled in the Art"*, 92 ISIS, 91 (2001); Luigi Palombi, *Gene Cartels*, supra, 36-91).

Allowing the patenting of chemical substances in the United States, producing very negative impacts of American industrialization prior to and during WWI, should be a reminder of the adverse impact of too liberal a patent policy in regard to isolated DNAs and cDNAs. And the concerns expressed by the Commissioner of Patents in *Ex Parte Latimer* Dec. Com. Pat 123 (1889) in the context of plant materials, made using a hypothetical example, are equally applicable here:

> The result would be that an alleged inventor in Germany would acquire a patent which would give him the exclusive use of *Pinus sylvestris*, the applicant in this case would secure a patent for the fibre of the *Pinus australis*, and thus, successively, patents might be obtained upon the trees of the forest and the plants of the earth, which of course would be unreasonable and impossible.

CONCLUSION

For the foregoing reasons, the petition for writ of certiorari should be granted.

Respectfully submitted,

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Counsel for Amici Curiae

AMICUS
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BRIEF

Supreme Court, U.S.
FILED

OCT 31 2012

OFFICE OF THE CLERK

No. 12-398

In The
Supreme Court of the United States

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ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

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On Petition For Writ Of Certiorari
To The United States Court Of Appeals
For The Federal Circuit

◆

BRIEF OF KALI N. MURRAY AND ERIKA R. GEORGE AS *AMICI CURIAE* IN SUPPORT OF PETITIONERS

◆

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INTEREST OF *AMICI CURIAE*

Kali N. Murray is an assistant professor of law at Marquette University Law School[1] Before teaching at Marquette, she practiced law at Venable, LLP, where she focused on patent litigation. Drawing upon her experience as a litigator, she teaches courses in patent law, intellectual property, international intellectual property, and property law. She has concentrated her academic research agenda on the varied players enforcing, governing, and participating in patent law, whether citizens, businesses, or the United States Patent and Trademark Office ("USPTO") as an administrative agency.

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[1] Counsel of record for all parties received notice at least 10 days prior to the due date of these *amici curiae*'s brief. Petitioners gave their blanket consent for *amici* to file briefs on October 12, 2012. Respondents consented to the filing of this brief on October 26, 2012. No counsel representing any party to the case authored this brief in whole or in part, and no counsel or party made any monetary contribution to the preparation or submission of the brief.

◆

SUMMARY OF THE ARGUMENT

The public's interest in the constitutional patent system is varied. An individual patent, like an invalid statute, can impose significant harm on a range of social interests. Among these social harms may be the communicative barriers imposed on the physician-patient relationship, the communicative barriers placed on researchers who seek to use the relevant information contained within a patent, and the communicative barriers placed on advocates who seek to ensure public health by disseminating information to impacted communities. Individual and organizational petitioners suffer and will continue to suffer, immediately significant injury from the wide scope of Myriad's patent claims, creating an actual controversy sufficient for them to bring suit under the Declaratory Judgment Act ("DJA").

The United States Court of Appeals for the Federal Circuit ("Federal Circuit"), therefore, erred below in two key respects. First, the Federal Circuit ignored this Court's clear and direct guidance in *MedImmune v. Genetech*, 549 U.S. 118 (2007), that a claim of patent invalidity must be examined under "all the circumstances" relevant to determining whether a live controversy exists under the Declaratory Judgment Act. *MedImmune,* 549 U.S. at 127 (*citing Maryland Cas. Co. v. Pacific Coal & Oil Co.*, 312 U.S. 270, 273 (1941); *cf. Muskrat v. United States*, 219 U.S. 346 (1911)). Second, the Federal Circuit has failed to recognize the significant threshold injuries suffered by the individual and organizational plaintiffs engaged in scientific, medical and public health pursuits when the ability to communicate crucial information and engage in inquiry is compromised. These specific injuries arise because Myriad's patents have received protection where none should exist. An authoritative testing of the validity of these patents under the common law exceptions to Section 101 of the Patent Act of 1952 ("Patent Act") is necessary to end the injury imposed upon individual and organizational plaintiffs who find that their ability to give and receive information under the First Amendment has been improperly impeded.

We respectfully urge the Court to grant certiorari to clarify proper standing analysis for declaratory judgment patent suits, with particular attention to the individual and organizational standing afforded to plaintiffs under Section 101 of the Patent Act.

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ARGUMENT

I. THE DECLARATORY JUDGMENT ACT SHOULD BE CONSTRUED TO PERMIT DIVERSE STAKEHOLDERS TO CHALLENGE INVALID PATENTS.

Those interested in a properly functioning patent system are many and varied: researchers engaging in cutting-edge scientific inquiry; manufacturers and designers implementing and selling these advances in the marketplace; and consumers putting these inventions and discoveries to use. While these diverse stakeholders benefit from the existence of disclosed valid patents, they can also be harmed by the existence of invalid patents.

The Federal Circuit's decision below erroneously constrains the needs of these diverse stakeholders. Its announced test imposes an improperly restrictive threshold injury on individual and organizational plaintiffs. Specifically, the Federal Circuit requires a declaratory judgment plaintiff to establish "injury in fact" by alleging both "(1) an affirmative act by the patentee related to the enforcement of his patent rights, *SanDisk Corp. v. STMicroelecs., Inc.*, 480 F.3d 1372, 1380-81 (Fed. Cir. 2007), and (2) meaningful preparation to conduct potentially infringing activity," *Cat Tech LLC v. TubeMaster, Inc.*, 528 F.3d 871, 880 (Fed. Cir. 2008).

The effects of the Federal Circuit's "affirmative act" test are far-reaching and profound. First, the "affirmative act" test appears to permit standing for only one category of impacted declaratory judgment plaintiffs, those individual plaintiffs impacted by the patentee's aggressive affirmative enforcement of his or her patent. Such a narrow test for standing undermines the remedial purposes of the Declaratory Judgment Act, which suggests that a flexible inquiry into "totality of circumstances" in order to determine whether or not declaratory relief is appropriate. Second, the "affirmative act" test appears to entirely preclude organizational standing within patent infringement context, by requiring that a declaratory judgment assessment be tied to the actions of an individual patentee, rather than the organization's goals or mission. Therefore, this Court's review is warranted.

A. The Declaratory Judgment Act Mandates a Flexible Case-Specific Inquiry As To Whether a Controversy Exists Between Relevant Parties.

The Declaratory Judgment Act permits "any interested party" to seek a court's declaration of "rights and other legal relations" whether or not "further relief is or could be sought" "[i]n a case of actual controversy." 28 U.S.C. § 2201(a) (2006). This Court requires that such a determination under the Declaratory Judgment Act requires "all the circumstances" to be considered when determining whether a live controversy exists between the parties, so to ensure an actual conflict exists that can be conclusively resolved through declaratory relief as opposed to a merely advisory opinion. *MedImmune*, 549 U.S. at 127 (*quoting Maryland Cas. Co. v. Pacific Coal & Oil Co.*, 312 U.S. 270, 273 (1941)). This determination under the Declaratory Judgment Act must meet the constitutional requirements of Article III of the U.S. Constitution. Therefore, a declaratory judgment plaintiff must prove that standing to bring the claim, among other constitutional requirements, such as ripeness and mootness. *See generally Lujan v. Defenders of Wildlife*, 504 U.S. 555 (1992).

The requirement that a declaratory judgment plaintiff must demonstrate an "affirmative act" of enforcement on the patent by the patent holder in order to show an "injury in fact" has been incurred is erroneous both under this Court's relevant precedent and under the remedial structure of the Declaratory Judgment Act. The Court's precedent in *MedImmune* mandates a full review of the relevant factual circumstances of each case, *on its own terms*. This flexible inquiry is the appropriate approach in determining whether or not a declaratory judgment plaintiff has constitutional standing. The Federal Circuit's substitution, of an inflexible test that curtails inquiry into all the circumstances of a case directly contradicts this Court's determination in *MedImmune*. In doing so, the Federal Circuit's decision below violated the letter of *MedImmune* – by refusing to consider "all the circumstances" attending justiciability – and the spirit of this Court's tradition of providing greater opportunities to challenge invalid patents. The "affirmative act" test is not only incompatible with this

Court's precedent; it is also incompatible with the role of the Declaratory Judgment Act in preserving a role in patent litigation for diverse patent stakeholders.

Our previous brief, Br. of Kali N. Murray and Erika R. George, 2012 WL 166994 (January 13, 2012), emphasized that the Declaratory Judgment Act serves to balance out a significant procedural advantage granted to a patent owner under § 281 of the Patent Act, 35 U.S.C. § 281 (2006), which allows the patentee to initiate an infringement claim. Consequently, under § 281 only the patentee has the power to initiate suit against potential infringers.

The Declaratory Judgment Act therefore exists as an integral alternative vehicle within the context of patent infringement because it permits diverse kinds of injury-in-fact to be alleged by diverse categories of declaratory judgment plaintiffs. The remedial structure of the Declaratory Judgment implies an inquiry into the standing of a respective plaintiff is not necessarily dependent on equivalent standing under the Patent Act.[2] For instance, in *United Food & Commercial Workers Local Union Number 137, et al. v. Food Employers Council Inc.*, 827 F.2d 519, 522 (9th Cir. 1987), the Court of Appeals for the Ninth Circuit ("Ninth Circuit") noted that standing for a declaratory judgment plaintiff can exist independently of the

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[2] An inquiry into appropriate subject-matter jurisdiction, however, is linked to the related statute. *Skelly Oil v. Phillips Petroleum*, 339 U.S. 667, 672 (1950).

"antitrust injury" required under Section 4 of the Clayton Act. The Court suggested that reading was possible as the textual commitments of the Declaratory Judgment Act create a declaratory remedy, which is available "whether or not further relief . . . could be sought." *Id.* at 523 (*citing* 28 U.S.C. § 2201(a)).

If, as the Federal Circuit desires, the "affirmative act" test is adopted as the sole test for establishing standing for declaratory judgment plaintiffs, a plaintiff would have to wait for the patentee to act in order to trigger a sufficient injury-in-fact under the Declaratory Judgment Act. This will force diverse declaratory judgment plaintiffs into a singular procedural posture, by always requiring them to allege that the patentee has acted in some way to harm the declaratory judgment plaintiff. This development would undermine the safety valve served by the Declaratory Judgment Act within the patent infringement. A singular test for standing based on the affirmative acts of declaratory judgment plaintiffs should not be the only test for standing of the declaratory judgment plaintiffs.[3] Rather such a test, ideally, would be one among many, undertaken with a precise eye on any given set of circumstances.

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[3] This is not to suggest, however, that the "affirmative act" test is without its own infirmities. For instance, its requirement of a narrow requirement that the patentee has undertaken an affirmative action may unnecessarily restrict standing where "a patent in a particular field creates a present risk to the ongoing economic activities of participants in that field." Br. of Intellectual Property Professors as Amici Curiae, 2012 WL 3643758, *3 (August 23, 2012).

A flexible inquiry into constitutional standing is especially appropriate within the context of patent law. Because of patent law's diversity of legal sources, including statutory, common law, and constitutional law, a range of patent disputes can be heard under the Declaratory Judgment Act. The typical declaratory judgment plaintiff does not want to be considered an infringer of a given patent and in a patent dispute will often allege that declaratory relief is needed since its potentially infringing acts will prompt the patentee to sue under § 281. The typical declaratory judgment plaintiff, therefore, suffers from a "mirror injury" insofar as the plaintiff's injury reflects the same type of injury suffered by patentee under § 281 – the harm caused by the existence of a potentially infringing act.

This is not to say that a typical declaratory judgment plaintiff is the ***only*** party that might be injured by the existence of an invalid or improperly granted patent. The remedial structure of the Declaratory Judgment Act permits a declaratory judgment plaintiff to allege harm that differs from a mirror injury that is raised by a potential infringer. In fact, this Court has recognized another type of injury suffered by a declaratory judgment plaintiff: those instances where there needs to be an "authoritative testing of patent validity" and with its accompanying "removal of restrictions on those who would challenge the validity of patents." *Blonder-Tongue Laboratories*

Inc. v. University of Illinois Foundation, 402 U.S. 313, 344-45 (1971). In those cases, it is evident that a patent can be invalid even where it is not infringed. This Court has suggested that a claim of validity can exist independently even after an infringement claim has been dismissed. For example, in *Altvater v. Freeman*, 319 U.S. 359, 363, 365 (1943), this Court held that "a decision of non-infringement . . . does not dispose of the counterclaim which raises the question of validity" in a case where a patent licensee acquiesced in paying royalties, though it did so "under protest." Likewise, in *Cardinal Chemical Co. v. Morton International*, 503 U.S. 83, 100 (1993), this Court held that an adjudication of patent non-infringement does not moot questions surrounding the non-infringed patent's validity.

This Court's precedent is illustrative of why the Declaratory Judgment Act may serve as an important vehicle to undertake an independent inquiry into the validity of a patent. Thus, it seems likely that a declaratory judgment plaintiff may challenge existence of an invalid patent under the Declaratory Judgment Act even where a claim for infringement does not exist under § 271 of the Patent Act. An inquiry into the validity of patent offers a way to examine issues of "greater public importance" in a way not afforded to a mere infringement claim, which seeks to adjudicate claims between two private parties. *Cardinal Chemical Co. v. Morton International*, 503 U.S. 83 at 100 (*quoting Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327 (1945)).

A required demonstration of mirror injury, therefore, is not appropriate in every circumstance. Rather, in those cases where authoritative testing of a patent's validity is required, it might be helpful to see the injury-in-fact suffered by a declaratory judgment plaintiff is equivalent to one harmed by an invalid statute: the mere existence of such patent can potentially threaten the legal interests of the harmed individual. *See* George W. Pugh, *The Federal Declaratory Remedy: Justiciability, Jurisdiction and Related Problems*, 6 Vand. L. Rev. 87, 88 (1952) ("It is suggested that the cases dealing with the interest requirement in fact break down into two broad groups: (1) those actions in which the decision will be of little if any immediate significance beyond the parties to the action and those in privity with them, and (2) those actions in which the decision will be of immediate significance beyond the immediate parties, as for example, actions involving the constitutionality of statutes or the validity of patents.").

Such claims, of course, are not without limit. A standing inquiry into a patent may turn on the same issues that confront a court that addresses whether a declaratory judgment plaintiff has been harmed by an invalid statute: "the appropriateness of the issues for decisions by courts and the hardship of denying judicial relief." *See Joint Anti-Fascist Committee v. McGrath*, 341 U.S. 123, 154 (1951) (Frankfurter, J., concurring). Indeed, not every patent will have an immediate significance beyond the particular concerns of the respective parties. However, some patents – like the patents at issue here, which claim in part, genetic materials that are the basic subject matter of human existence – will have immediate significance to a range of social interests. A patent may have immediate significance when, as with those patents at stake here, such patents cause harm by limiting access to the basic building blocks of nature and scientific inquiry, or by blocking the free flow of information, both a speaker's right to communicate technical information and the listener's right to receive and benefit from that information. *See, e.g.*, *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748 (1976).

The injuries at stake in this declaratory judgment action are not abstract. In particular, in our previous brief, we noted that the existence of Myriad's invalid patents impose significant social costs on communications embodied within their respective patents. Some individual plaintiffs suffered immediately significant harm in their ability to access health care and services. For instance, two of the patient-plaintiffs here, Lisbeth Ceriani and Patrice Fortune, have felt this harm firsthand. (Fed. Cir. App'x at A1043, A1045.) Despite their health coverage under a low-income Medicaid insurance program, Myriad denied their request for testing by refusing their insurance. (*Id.*) Both Ms. Ceriani and Ms. Fortune lack the financial resources to pay for this testing out of pocket. (*Id.*)

Other individual plaintiffs suffer from the inability to discuss relevant medical information. Individual physicians and plaintiffs are seeking to share information about the predisposition to breast or ovarian cancer allege they have been constrained by an improvidently granted federal patent that permits Myriad to enforce its legal interests that are adverse to those of the plaintiffs. (*See, e.g.*, Fed. Cir. App'x at A1284.) While researchers and physicians would like to offer gene testing, they are ultimately constrained by patent restrictions. (*See, e.g.*, *id.* at A149; A151; A1284.) Patients are left to make decisions on their own from a position of uncertainty without the benefit of full information because of various barriers to accessing the genetic testing offered exclusively through Myriad. (*See, e.g.*, *id.* at A20-A25; A1594-A1595; A1598-A1599; A1602-A1603; A1606-A1607; A1610-A1611; A1614-A1617; A160; A2652; A2937-A2938; A3065; A3072-A3073; A3077; A2851).

These harms, of course, impact the individual plaintiffs, but they also cause harms that are of immediate significance to others that are not involved in this case. The grant of the Myriad patents has imposed a collective social tax in excess of their individual usefulness, and therefore, provides an important example of why "harm" in patent law in all of its statutory, constitutional, and common-law forms, must be served by a flexible inquiry under the Declaratory Judgment Act.

B. The Declaratory Judgment Act Flexible Inquiry Should Afford Standing to Individual and Organizational Plaintiffs.

The law on organizational standing is well established and affords organizations two types of standing. "An association has standing to bring suit on behalf of its members when its members would otherwise have standing to sue in their own right, the interests at stake are germane to the organization's purpose, and neither the claim asserted nor the relief requested requires the participation of individual members in the lawsuit." *Friends of the Earth, Inc. v. Laidlaw Environmental Services*, 528 U.S. 167, 181 (2000). Further, "an organization has standing on its own behalf if it meets the same standing test that applies to individuals. The organization must show actual or threatened injury in fact that is fairly traceable to the alleged illegal action and likely to be redressed by a favorable court decision." *Spann v. Colonial Village, Inc.*, 899 F.2d 24, 27 (D.C. Cir. 1990).

The Federal Circuit's reliance on the "affirmative acts" test is, therefore, in error because it essentially precludes a claim of organizational standing under the Declaratory Judgment Act in two key respects. First, the Federal Circuit's "affirmative acts" test mandates that declaratory judgment plaintiffs can claim standing only in those instances where the patentee has undertaken steps that suggest they are likely to sue for potential infringement. As discussed, *supra*, this precludes a claim of relief for those individuals harmed by the existence of an invalid patent. It follows, then, that any organization representing one of these individual members, would not have standing under this restrictive test. Second, in the same respect, this restrictive test would preclude independent organizational standing insofar as such organizations would not be able to claim that their organizational mission was harmed by the existence of an invalid patent. For example, the claims of an entity like Breast Cancer Action, a national education and activist organization that exercises its First Amendment rights when it seeks to "transform breast cancer from a private medical crisis to a public health emergency" could not be brought. (A1402) Similarly, the Boston Women's Health Book Collective engages in education and advocacy and publishes information about public health and genetic analysis. (A1042-A1043).

Central to the missions of both these organizations is communicating information that pertains to the health and welfare of the public. Genetic counselors within these organizations would serve as the messengers of crucial health information, were their First Amendment rights not curtailed by the existence of an invalid patent. *See, e.g.*, Alexandra Minna Stern, *Telling Genes: The Story of Genetic Counseling in America* (2012) (assessing the role of genetic counseling in public health communications). The Federal Circuit offers no independent reason for why public interest organizations within patent law should be constrained in so crippling a manner.

◆

CONCLUSION

Patent policy depends on its caretakers. When invalid patents stifle the patent system's goals, it falls on patent law's enforcers to police its boundaries. This Court's generalized review is therefore warranted and necessary. It is, therefore, appropriate in those circumstances that a court examine whether the declaratory judgment plaintiff has been impacted by the existence of the invalid patent. Maintaining the existence of this possibility under the Declaratory Judgment Act is vital since the Federal Circuit has denied various plaintiffs' claims under the Administrative Procedure Act against the Commissioner of the USPTO, deciding that associations and individuals suing in one case had not alleged injuries within the "zone of interests" contemplated by the Patent Act, *Animal Legal Defense Fund v. Quigg*, 932 F.2d 920, 937-38 (Fed. Cir. 1991), and closed access to a third-party requester in *Syntex (U.S.A.) Inc. v. USPTO*, 882 F.2d 1570, 1571 (Fed. Cir. 1989). For third parties to have any recourse against the injuries caused to their rights by invalid patents, the Declaratory Judgment Act must be allowed to operate as the crucial safety valve that this Court has indicated it is.

Respectfully submitted,

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AMICUS
CURIAE
BRIEF

No. 12-398

IN THE

Supreme Court of the United States

ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF *AMICI CURIAE* OF THE NATIONAL WOMEN'S HEALTH NETWORK, REPRODUCTIVE HEALTH TECHNOLOGIES PROJECT, DISABILITY RIGHTS LEGAL CENTER, FORWARD TOGETHER, THE CENTER FOR GENETICS AND SOCIETY, THE PRO-CHOICE ALLIANCE FOR RESPONSIBLE RESEARCH, ALLIANCE FOR HUMANE BIOTECHNOLOGY, G. MICHAEL ROYBAL, MD, MPH, AND ANNE L. PETERS, MD IN SUPPORT OF PETITIONERS

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INTEREST OF *AMICI CURIAE*

Amici Curiae are health and social justice advocates, experts in policy issues concerning women's health, and health disparities for socio-economically disadvantaged women and women of ethnic and racial backgrounds. *Amici Curiae* educate community-based organizations about the implications of genetic technologies for women's health, and advocate for just public policy. *Amici Curiae* also include physicians/researchers working in our burdened healthcare system, experts in the clinical care and treatment of underserved populations they understand the importance of genetic technologies for preventative medicine, treatments, and potential cures.

Amici Curiae are deeply concerned about the Federal Circuit's decision to allow the patenting of the BRCA 1/2 genes. *Amici* understand that Myriad's patents monopolize molecules and genes that embody essential scientific principles, and recognize that the preemption of this knowledge inhibits innovative work in research and treatments for breast and ovarian cancer, with resultant harms for the communities and patients they serve.[1]

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[1] The parties have consented to the filing of this brief and letters of consent to the filing were lodged with the Clerk of the Court. Counsel of record for all parties received timely notice of *amici curiae's* intention to file this brief, per Supreme Court Rule 37. No counsel for a party authored this brief in whole or part, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amici curiae* and their members or their counsel made a monetary contribution to its preparation or submission.

Amicus Curiae **The National Women's Health Network** aspires to a health care system that is guided by social justice and reflects the needs of diverse women by developing and promoting a critical analysis of health issues which affect policy and support consumer decision-making, providing evidence-based information free from corporate influence. They have particular expertise in women's health issues as a result of their research and evaluation of emerging drugs, devices, and treatments and their impact on women's health.

Amicus Curiae **Reproductive Health Technologies Project** is a national non-profit organization working on behalf of every woman to achieve access to the safest and most effective methods for protecting their health, by ensuring that new technologies are developed and introduced with appropriate safeguards, a well-informed consumer constituency, and broad based public support. Bringing together experts, using solid science and clinical data to influence political outcomes, and seeking consensus among diverse communities, RHTP is a powerful vehicle for public education and policy development around health technologies.

Amicus Curiae **Disability Rights Legal Center** champions the rights of people with disabilities through education, advocacy, and litigation. Together with the Loyola University School of Law at Los Angeles, they direct the **Cancer Legal Resource Center**. Since 1997, the CLRC has provided free information and resources on cancer-related legal issues to cancer survivors, caregivers, health care professionals, employers, and others coping with cancer, serving over 310,000 people through conferences, seminars, workshops, education and outreach programs, and other cancer community activities. To this end, the CLRC runs a free and confidential national Telephone Assistance Line that assists individuals with cancer and genetic-related legal issues, including the costs of testing, insurance coverage, employment, and access to health care and government benefits.

Amicus Curiae **Forward Together** is a nonprofit community-based multi-racial organization that engages in grass-roots action and training community leaders, working in communities of color to ensure that women and adolescents have the information they need to improve their own health status, and believing in policy that enables *all* people to have the economic, social, and political power and resources necessary for decision-making regarding their bodies.

Amicus Curiae **The Center for Genetics and Society** is a nonprofit public affairs organization working to encourage responsible uses and effective societal governance of genetic, reproductive and biomedical technologies. Providing accurate information regarding these technologies to the public, CGS works with civil society leaders, health professionals, scientists, and others who share a commitment to advancing the public interest in the development of policy regarding human biotechnologies.

Amicus Curiae **The Pro-Choice Alliance for Responsible Research** is a coalition of reproductive rights and justice advocates, bioethicists, academics, and community leaders promoting accountability, safety and social justice in bio-medical research from a women's rights perspective. Since 2004, PCARR has been providing research and legal analysis to policymakers and consumers, and engaging with administrative agencies to ensure that women's health outcomes are protected in the implementation of new biotechnologies.

Amicus Curiae **Alliance for Humane Biotechnology** is a non-profit association that conducts outreach and education on the social implications of human genetics and works for a culture of science that places the health and welfare of people above financial interests.

Amicus Curiae **G. Michael Roybal, MD, MPH** is the Medical Director of the Roybal Comprehensive Health Center (CHC), established to address the inequity of communities and individuals without access to affordable healthcare. Dr. Roybal has spent his career working with the Department of Health Services for Los Angeles County, focusing on healthcare redesign and reform in an attempt to improve healthcare delivery for underserved populations.

Amicus Curiae and **Anne L. Peters, MD**, is the Director of the Diabetes Clinic at the Roybal Comprehensive Health Center (CHC) and a Professor at the USC Keck School of Medicine. An internationally known expert in the field of treatment for diabetes, she has received numerous grants to improve health environments and reduce obesity rates in underserved populations. Her work at the CHC provides over 80,000 yearly patient visits, mostly for the uninsured. A similar program she developed is situated at five additional safety-net sites in Los Angeles County.

SUMMARY OF ARGUMENT

This Court recently considered the nature of exceptions to the categories of patentable subject matter according to 35 U.S.C. §101, *Mayo v. Prometheus*, 132 S. Ct. 1289 (2012), and ordered that this case be remanded in light of *Mayo* and its foundational principles. *Association for Molecular Pathology, et al., Petitioners, v. Myriad Genetics, Inc., et al,* ___ U.S. ___, 132 S. Ct 1794, 182 L. Ed.2d 613 (2012). Deciding the patent eligibility of a claim to a diagnostic process, *Mayo* clarified the law/product of nature doctrine by explaining what necessitates turning a patent-ineligible law of nature into a patentable application of that law. *Mayo* at 1289. *Amici* argue that the Federal Circuit failed to apply the essential principles delineated in *Mayo* to the issue of whether isolated DNA/cDNA molecules are exceptions to the statutory categories, and that the allowance of Myriad's patents on the BRCA 1/2 genes results in grave harms for the health of women and their families particularly those who are socio-economically disadvantaged or of ethnic or minority backgrounds.

This Court in *Mayo* described the nature of the medical diagnostic method at issue as a relationship, a law of nature, *id.*, 132 S. Ct. at 1297, as nothing of significance had been added to the underlying natural phenomenon to make it a patentable application of that law. *Id* at 1297-1300. Significantly, *Mayo* considered the patents' preemptive effect relevant to their conclusion that the resultant inhibition of innovation rendered the process ineligible for patent protection. *Id.*at 1302.

Amici argue that *Mayo's* analysis is equally applicable to a composition claim. Myriad's patents on the BRCA

1/2 genes are for phenomena of nature analogous to the claimed relationship in *Mayo*. Lacking an inventive concept, nothing of significance has been added to the law/product of nature itself to render it patent-eligible. Myriad's claims to the isolated DNA/cDNA molecules of those genes simply describe natural phenomena which are not markedly different whether inside or outside the human body.

The Federal Circuit stated that the case was *not* about whether those at increased risk of breast cancer were entitled to second opinions, whether one company should hold a patent or license covering a test which may save people's lives, or whether other companies should be excluded from a market encompassed by such a patent. *Association for Molecular Pathology v. United States PTO*, 2012 U. S. App. LEXIS 17679, 50 (August 16, 2012). *Amici* disagree, and argue that these examples illustrate *Mayo's* essential concern: patents which preempt too much future use of laws of nature inhibit and impede innovation.

Myriad's patents on isolated DNA/cDNA molecules preempt the use of laws of nature regarding the human genome. Giving a cancer patient a second opinion based upon the vital genetic informational content of the BRCA 1/2 genes is *an infringement on Myriad's patents*. Only one company, Myriad, can use these scientific principles which contain keys to saving lives, *otherwise an infringement on Myriad's patents has occurred*. Excluded from the market, and the marketplace of ideas, scientists, researchers, workers in biomedical communities, clinicians, and patients attempting to study and use these scientific tools *infringe Myriad's patent claims*. These patents foreclose innovation in biomedical research and healthcare causing grave harms for the health of women and their families, particularly those who are socio-economically disadvantaged or ethnic and racial minorities.

The important principles delineated in the *Mayo* decision are applicable to the case at bar. Myriad's claims are for patent-ineligible laws and products of nature and should be invalidated.

ARGUMENT

I. *Mayo* Controls the Issue of the Patentability of Myriad's Claims.

The Federal Circuit erred by failing to apply the enunciated principles of *Mayo* to the issue in the present case, whether Myriad's patent claims to isolated DNA/cDNA molecules are patent-ineligible exceptions to the statutory categories, or patent-eligible compositions of matter according to 35 U.S. §101. *Ass'n*, 2012 U.S. App LEXIS 17679 at 51.

"Laws of Nature, natural phenomenon, and abstract ideas are not patentable subject matter under §101 of the Patent Act." *Mayo*, 132 S. Ct. at 1293, citing *Diamond v. Diehr*, 450 U. S. 175, 185, 101 S. Ct. 1048, 67 L. Ed. 2d 155 (1980). Additionally, "phenomenon of nature, though just discovered... are not patentable, as they are the basic tools of scientific and technical work." *Id.*, citing *Gottschalk v. Benson*, 409 U. S. 63, 67, 93 S. Ct. 253, 34 L. Ed. 2d 273 (1972). *Mayo* acknowledged that "monopolization of those tools through the grant of a patent might tend to impede innovation more than it would tend to promote it." *Mayo*, *supra*.

Mayo considered whether a process for measuring the relationship between concentrations of metabolites in the blood and a likelihood that a certain dosage of drug would prove effective or cause harm, was patent-eligible subject matter. *Id.*,132 S. Ct. at 1296. Despite administering a drug to trigger the manifestation of the relationship, the relationship existed apart from any human action and was an entirely natural process. *Id.* at 1296-97. The claims did not rest upon inventive concepts as nothing in the steps of the process added anything of significance to the law of nature itself. *Id.* at 1298. The process was essentially for the underlying relationship, a patent-ineligible law of nature. *Id.* at 1302.

Mayo recognized that patenting basic scientific tools posed a danger for future innovation, particularly if more future innovation was foreclosed than justified by the underlying discovery. *Id.* at 1301. Although the claimed law of nature in *Mayo* was narrow, these concerns were implicated, affecting the ability of doctors to determine treatment options and threatening the development of more refined treatment recommendations which would combine features of the correlation with later discoveries involving aspects of human physiology and biology. *Id.* at 1302. This preemption of future uses of laws of nature reinforced this Court's conclusion that the processes were not patent eligible. *Id.*

The Federal Circuit erred in its application of *Mayo* by resting on two premises: 1) the isolated DNA/cDNA molecules were compositions of matter not processes, therefore *Mayo* did not control the issue of patent eligibility; and 2) the isolated molecules were not products of nature. *Ass'n*, 2012 U. S. App. LEXIS 17679 at 51-55. In light of *Mayo*, patent claims on isolated DNA/cDNA are directed to patent-ineligible laws and products of nature.

Myriad's claimed molecules of the BRCA 1/2 genes are the embodiment of important information and pre-existing scientific principles; both their structure and function encodes the relationship between a DNA molecule and a protein. The patent claims disclose the sequential information embodied in the molecules, they merely describe this relationship and do not add any inventive concepts to this underlying law and product of nature. Isolating and synthesizing these molecules do not change their identity, despite minute structural changes they are not markedly different from what is found in nature.

These molecules are analogous to the law of nature delineated in *Mayo* as well as products of nature. Myriad's patents preempt basic scientific knowledge and tools, tie up too much of their future use, and impede rather than promote innovation. In accordance with *Mayo*, this Court should grant certiorari to correct the Federal Circuit's flawed decision and hold these claims ineligible for patent protection.

A. Isolated DNA/cDNA Molecules of the BRCA 1/2 Genes are Laws of Nature:

The process in *Mayo* claimed a correlation, primarily a relationship between concentrations of metabolites in the blood and the likelihood that a certain dosage of drug would prove effective or cause harm: "The relation is a consequence of the ways in which thiopurine compounds are metabolized by the body-entirely natural processes." *Mayo*, 132 S.Ct. at 1297. Despite the human action of administering a drug to manifest the relation, "a patent that simply describes that relation sets forth a natural law." *Id.* at 1298.

The embodied informational content of the claimed isolated DNA/cDNA molecules is similarly, a relationship, a law of nature. DNA is a chemical molecule composed of four standard repeating chemical units, adenine, thymine, cytosine and quinine (aka, A, T, C, G) known as nucleotides, or bases. *Ass'n for Molecular Pathology v. United States PTO*, 702 F. Supp. 2d 181, 193 (S. D. N. Y. 2010). The ordering of these bases is described as nucleotide sequences, DNA sequences or gene sequences. *Id.* at 194. Gene sequences constitute biological information, describing the structural and chemical properties of a particular DNA molecule that is the cellular "blueprint" for the productions of proteins, and are of a double nature: they are both "chemical substances of molecules as well as physical carriers of information, i.e., where the actual biological function of this information is coding for proteins." *Id.* at 194, 228, citing Strauss Decl. at P 20.

For patenting purposes, it is the structures themselves which are useful. *See,* Dan Burk, *The Problem of Process in Biotechnology*, 43 Hous. L. Rev. 561, 582-87 (2006). The interest is not in the string of 'letters' of the sequence, but "in…building informational structures-the molecules that are the conduit for information transfer." *Id.* at 586-87. These informational structures are the sole content of Myriad's isolated DNA/cDNA claims, the embodiment of the specified nucleotide sequences relating to the BRCA 1/ 2 genes. *See,* e.g. claims 2, 5, 6, 7 of U. S. Patent No. 5,747,282; claims 1, 6, 7 of U. S. Patent No. 5,837,492. *Id.* at 212; Claim 1 of the '282 patent is for "1) An isolated

DNA coding for a BRCA-1 polypeptide[protein], said polypeptide having the amino acid sequence set forth in SEQ ID NO: 2." U.S. Patent No. 5,747,282 col. 154 11.56-58 (filed June 7, 1995).

This ordering of the chemical bases, the arrangement of nucleotides is a relationship, an entirely natural process. The structure of the nucleotides in the molecule enables the instructions for the building of proteins in the human body, or within identical and synthesized DNA. The ordering is a pre-determined relationship, a correlation that reveals a genetic susceptibility to breast and ovarian cancers in the BRCA 1/2 genes, a pre-existing scientific principle. The relationship remains unchanged apart from the human action of isolation or synthesis. The claims "simply describe the relations" between the order of the nucleotides and their resulting chemical, structural, and functional content. The claims merely "point out a set of facts that exist in the world…" *Mayo v. Prometheus*, 2011 U. S. Trans. LEXIS 76 *39, *43 (2011). As such they are patent-ineligible laws of nature.

B. Claims to Isolated DNA/cDNA Molecules do not Contain Inventive Concepts and are Patent-Ineligible Products of Nature.

Processes using a natural law must also contain an inventive concept so that the patent is "significantly more than a patent upon the natural law itself." *Mayo*, 132 S. Ct. at 1294. The steps in *Mayo's* claimed process--administering, determining, and a wherein step-- simply told doctors to gather data and draw inferences in light of the correlations. *Id.* at 1298. The steps were well understood, routine, conventional activity already engaged in by the scientific community. *Id.* The claims were not transformative, and did not make a claimed law of nature a patentable application of that law. *Id.*

Claims to isolated DNA/cDNA molecules do not rest on inventive concepts. The claim terms indicating isolation or synthesis do not add anything of significance to render these laws and products of nature patent-eligible. "Isolated" simply denotes "a nucleic acid…which is substantially separated from other cellular components which naturally accompany a native human sequence." *Ass'n*, 702 F. Supp at 213, n.30. Having been derived from mRNA, a synthesized cDNA molecule represents an exact copy of one of the protein coding sequences encoded by the original genomic DNA. *Id.* citing Leonard Decl. P 75.

Well-established laboratory techniques are used in isolating, extracting the claimed molecules from their cellular environment. *Id.* at 198. DNA sequencing processes used to determine the ordering of the nucleotides within a DNA molecule are well known techniques understood and routinely performed by scientists skilled in molecular biology. *Id.* at 200. These conventional activities add nothing to the phenomena of nature itself.

Disregarding *Mayo*, the Federal Circuit relied on the test established in *Diamond v. Chakrabarty*, 447 U. S. 303, 100 S. Ct. 2204, 65 L. Ed. 2d 144 (1980) to determine that the claimed molecules were "markedly different" from what existed in nature, and thus patent-eligible. *Ass'n*, 2012 U. S. App, LEXIS 17679 at 56-61. The court reasoned that while DNA molecules exist in the body (native DNA) as part of a "large structural complex," (i.e., part of a chromosome), isolated DNA is "a free standing portion of a larger natural DNA molecule," which had been cleaved (i.e., had covalent bonds in its backbone chemically severed, or synthesized to consist of just a fraction of a naturally occurring DNA molecule). *Id.* at 61-62. Resulting from this cleavage or synthesis, the isolated DNA/cDNA was declared a distinctive chemical identity, and thus "markedly different" from patent-ineligible products of nature. *Id.*

The minute change in physical structure does not make the isolated or synthesized molecules, "*markedly* different" from their native state or impart a distinctive identity. Rather, the Federal Circuit dismissed established biological truths regarding the functionality of the molecules. *Id.* Unlike other chemicals, the molecules describe the nucleotide sequences which direct the proteins, cells and organs which make up the body. This biological function is the defining and identical characteristic of DNA/cDNA both before and after isolation or synthesis, and thus, these molecules are not markedly different from their native state. In fact, if these isolated or synthesized molecules had a truly distinctive chemical identity or were markedly different from what exists in nature their applications in research and diagnostics could not use the natural biological characteristics of DNA sequences to code for a protein and to anneal to its complementary nucleotide sequence. Products of nature, they "...serve the ends nature originally provided." *Funk Bros. Seed Co v. Kalo Inoculant Co.,* 333 U. S. 127, 131, 68 S. Ct. 440, L. Ed. 588 (1948).

Myriad's claims do not rest upon inventive concepts, as the techniques of isolation and synthesis are not transformative.

C. Myriad's Patents Preempt Phenomena of Nature, Inhibiting Innovation and Limiting Future Discoveries in Biomedical Research and Development.

A patent is a right which allows the exclusion of others from making, or using the patented invention. 35 U.S.C. § 271(a) (2000). This Court has repeatedly emphasized the concern that "patent law not inhibit further discovery by improperly tying up the future use of laws of nature," as this might impede, rather than promote innovation. *Mayo*, 132 S. Ct. at 1301.

This Court's precedents, "...warn us against upholding patents that too broadly preempt the use of a natural law." *Id*, citing *O'Reilly v. Morse*, 56 U.S. 62, 14 L. Ed. 601 (1854). Examples include general claims for underlying scientific principles, *id*, abstract and sweeping claims to a mathematical formula which covered both known and unknown uses of that formula, *id*, citing *Benson*, 409 U.S. at 67, 93 S. Ct. 253, 34 L. Ed. 2d 273, concepts involving business transactions which precluded the use of its approach in all fields, *id*, citing *Bilski v. Kappos*, 130 S. Ct. 3218, 177 L. Ed. 2d 792 (2010), and a formula that could be preempted from use in a broad range of possible uses. *Id*, citing *Parker v. Flook*, 437 U. S. 584, 586, 98 S. Ct. 2522, 57 L. Ed. 2d 451 (1978).

Although the process claimed in *Mayo* was a narrow law it implicated these concerns. *Mayo*, 132 S. Ct. at 1302. "It told a doctor to measure metabolite levels and to consider them in light of the statistical relationships they describe," *id*, so that relationship cannot be used by doctors in subsequent treatment decisions to determine whether or not the treatment should change. *Id.* The correlation cannot be used to develop more refined treatment options when combined with "later discovered features of metabolites, human physiology or individual patient characteristics." *Id.* The recognition that the "patents tie up too much future use of laws of nature" reinforced the Court's conclusion that the process was not patent-eligible. *Id.*

Myriad's patents on isolated DNA/cDNA "too broadly preempt natural laws." They are "general," preempting *all uses* of fundamental principles of molecular biology and genetics. The claims are "sweeping" covering both "known and unknown uses" of the embodied information of the BRCA 1/2 genes, preempting this knowledge from all fields of biomedical research and healthcare, including a broad range of potential uses for diagnosing and treating breast and ovarian cancer.

Specific claims are illustrative. Claim 5 of the '282 patent covers any isolated DNAs "having at least 15 nucleotides" of the BRCA 1 gene, thus the claim covers the entire BRCA 1/ 2 genes. The patents cover both known and unknown mutations for increased susceptibility to breast and ovarian cancer, e.g., Claim 6 of the '492 patent is "directed to any DNA nucleotide encoding any mutant BRCA 2 protein that is associated with breast cancer," including all possible mutations and variations found within those genes. These patents give Myriad the right to exclude anyone from using the DNA of the BRCA 1/2 genes, or copies of these genes outside the human body. The patents restrict all research and clinical testing of the BRCA 1/2 genes. Unlike patents on new drugs, no one can "invent around" Myriad's patents as one cannot invent a molecule of DNA which encodes the protein which embodies the genetic information of an individual's BRCA 1/2 genes.

The practical implications of this broad preemption inhibit rather than promote progress and innovation. Because Myriad's patents give them a monopoly on genetic testing for breast and ovarian cancer in the United States, like the physicians in *Mayo* unable to change their treatment options, physicians in our country cannot give second opinions regarding a diagnosis for the disease. Like the physicians in *Mayo* unable to refine their treatment methods, physicians treating breast and ovarian cancer are unable to refine their treatment methods because basic biomedical research and research and the development of alternative genetic testing methods have been restricted by Myriad's monopolies on the BRCA 1/ 2 genes. These patents have limited scientific discoveries and will continue to inhibit innovation.

Clinical researchers and laboratory directors have expressed real fears that they will be prevented from doing their work by patent holders. *See,* Richard Gold and Julia Carbonne, *Myriad Genetics: In the Eye of the Policy Storm,* 12 Genetics in Medicine S39 (2010) [hereinafter "Gold"]. These patents negatively affect follow-on public research about the BRCA genes as researchers forego about one in ten research publications as a result. *See Secretary's Advisory Committee on Genetics, Health & Society: Gene Patents and Licensing Practices and their Impact on Patient Access to Genetic Tests,* 4-2010, at A-27[hereinafter "*Report*"].

Ambiguity regarding the possibility of infringement liability inhibits innovation, as scientists avoid work, or "are wary of public reporting results." *Id.* Myriad has not clarified the concept of "infringing activities," or publicly confirmed in writing, their assertion that their patents are not enforced against researchers. *Id.* at A26-27.

Scientists expressed concerns about contributing their research on the BRCA genes to public databases. Gold, *supra* at S44. A university researcher was specifically told *not* to contribute his findings of new mutations. *Id.* In 2004, Myriad stopped contributing data concerning "variations of unknown significance" (VUS) accumulated as a result of their exclusive testing, to the NIH open access Breast Cancer Information Core mutation database, and ceased publishing information regarding these important discoveries in peer-reviewed literature, significantly impeding research. John Conley, Dan Vorhaus, Robert Cook-Deegan: Genomics Law Report, March 1, 2011: *How Will Myriad Respond to the Next Generation of BRCA Testing, available at* http://www.genomicslawreport.com/index.php/2011/03/01/how-will-myriad-respond-to-t.

Myriad is the sole provider of genetic testing in the U.S., and has stopped other laboratories from genetic testing. *Report* at 40. Due to the breadth of Myriad's patents, the development of alternative or improved testing methods is diminished. 53% of clinical laboratories do not develop new or improved genetic tests, Mildred K. Cho, et al., *Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Service,* 5 J. Molecular Diagnostics, 3, 5 (2003), and researchers have stated that Myriad prevented the development of improved BRCA 1/2 tests. See Gold, *supra* at S44. Any research resulting in a commercial or clinical service infringes Myriad's patents, notably "...the assessment of technology by third parties, e.g. to evaluate a test for sensitivity, specificity, or positive predictive value." See, Ozdemir, et al, *Shifting Emphasis from Pharmacogenomics to Theragnostics*, Nature Biotechnology, Vol. 24 No. 8 (2006).

Myriad's patents inhibit future innovation in the area of personalized medicine, whose development rests upon genotype-phenotype associations (e.g. BRCA 1/2 mutations and the susceptibility to breast and ovarian cancer). *See*, Roger D. Klein, MD, JD, *Gene Patents and Personalized Medicine*, 2012, American Society of Clinical Oncology. New methods of testing for these associations, able to detect millions of genetic variations and mutations in thousands of genes or even the entire genome will guide treatments, drug dosages and prevention for numerous diseases. However, "If we are to enter the next stage of personalized medicine, we cannot do so by parceling out information-genomes do not work that way, pleiotropy... doesn't stop at the lines drawn by the USPTO." Zachary Russ, *The Holes in Whole Genome Sequencing*, Genetic Engineering & Biotechnology News, *available at:* http://www.genengnews.com/blog-biotech/the-holes-in-whole-genome-sequencing/676 .

"Patent thickets, blocking patents, and high transactions costs" threaten the use of these next generation innovations in genetic testing, such as whole genome sequencing (WGS). *Report* at 50-51. Fearing liability, laboratories using multiplex tests are not reporting results to patients or sending clinicians the results of tests involving patent protected genes. *Id.* Broad patents such as Myriad's isolated DNA/cDNA claims create uncertainty leading to high transaction costs. WGS industries may need to examine specific patent claims for "all or many of the thousands of human genome sequences subject to patent protection." Dan Vorhaus and John Conley, Genomics Law Report, *Whole Genome Sequencing and Gene Patents Coexist (For Now)*, August 11, 2009, available at: http://www.genomicslawreport.com/index.php/2009/08/11/whole-genome-sequencing-and. The patents potentially affect the use of WGS in assessing for risk or existence of disease, and thus, patient care. National Society of Genetic Counselors, Position Statement of Human Gene Patents, available at: http://www.nsgc.org/Advocacy/PositionStatements/tabid/107/Default.aspx (2010).

Exome sequencing, targeted sequencing restricted to the protein-coding subset of human genes, is based upon an "enrichment of targeted DNA regions by hybridization with probes." Patricia F. Dimond, PhD, *Exome Sequencing Finds Sweet Spot Between Whole-Genome and Targeted Sequencing*, Genetic Engineering & Biotechnology News, *available at*: http://www.genengnews.com/keywordsandtools/print/3/25217/ . The technique's costs relating to data collection, storage and analysis are significantly less than those in WGS techniques, and also lead to the discovery of highly pertinent variants. *Id.* However, "exome sequencing is more likely to face IP issues....because gene patents typically cover methods that would specifically target or enrich for the gene." Monica Heger, *Interpretation Remains Key Challenges in Clinical Sequencing; Patents May Impede Return of Results.* Genome Web, June 27, 2012. Available at: http://www.genomeweb.com/print/1096581.

The potential for infringement using these new methods could "slow some promising clinical technologies." Subhashini Chandrasekharan and Robert Cook Deegan, *Gene Patents and Personalized Medicine, what Lies Ahead?* Genome Medicine, 2009, 1:92. For example, holdout problems might result when drug manufacturers creating targeted therapies "do not own the underlying molecular pathological relationships." Klein, *supra* at 82.

Myriad's patents illustrate these concerns. Numerous cancer patients with BRCA 1/ 2 mutations have a negative family history, and do not qualify for testing according to Myriad's criteria. Walsh, Lee, Casadei, Thorton, Stray, Pennil, Nord, Mandell, Swisher, and Mary-Claire King; PNAS Early Edition, *Detection of Inherited Mutations for Breast and Ovarian Cancer Using Genomic Capture and Massive Parallel Sequencing,* www.pnas.org/cg/10.1073/pnas [hereinafter "King"]. However, the development of specific treatments, inhibitors which effectively kill BRCA 1/2 mutated carcinomas having *therapeutic* as well as preventive applications, necessitates an increased need for identifying BRCA 1/ 2 mutations in women with breast and ovarian cancer through testing, which is restricted by Myriad's exclusive test on the patented sequences. *Id.*

The monopolization of the BRCA 1/2 genes tie up too much of their future use. The resultant inhibition of innovation in biomedical research and healthcare treatment is not justified by Myriad's original discovery.

II. Myriad's Patents Diminish the Availability and Quality of Healthcare for Women and their Families, Particularly Those Who are Socio-Economically Disadvantaged, and/or Ethnic or Racial Minorities.

Myriad's patents have implications for the health of women and their families. While the average woman in this country has around a 12%-13% risk of developing breast cancer in her lifetime, women with BRCA mutations face a cumulative risk of between 50% - 80% for breast cancer and a 20%-50% cumulative risk of ovarian cancer. *Ass'n.*, 2012 U. S. App. LEXIS at 18. Testing for BRCA mutations is critical for decisions regarding clinical care, including surgical and therapeutic options. *Id.* at 18-19.

Patent monopolies on human genes eliminates competition, likely resulting in higher prices, diminished patient access, and decreased quality in genetic testing. See Klein, *supra* at 82. Generally, patients have greater access to genetic tests within competitive markets. Andrew S. Robertson, *The Role of DNA Patents in Genetic Test Innovation and Access,* 9 Nw. J. Tech. & Intell. Prop. 377 at 397-98. Myriad prohibits identifying and allowing researchers to provide numerous, alternative testing methods, including those which are potentially more efficient and cost effective. Robert Cook-Deegan, Subhashini Chandrasekharan & Misha Angrist, *The Dangers of Diagnostic Monopolies,* 458 Nature 405 (2009). Costs per mutation were five times as high using Myriad's test than those developed and used in Europe. *Report* at A-27. Myriad's patents deny a patient access to a confirmatory test from a different laboratory, even when initial tests are inconclusive. *Id.*

Myriad's patents restrict the development of improvements in the quality of genetic tests. Clinical geneticists outside of Myriad's laboratories cannot determine the accuracy of Myriad's test in identifying mutations in the BRCA genes or predicting a patient's risk for breast or ovarian cancer. Using Myriad's test, non-clinical researchers found 10-20% of false negatives in high risk patients. Walsh T., Casadei S., Coat KH et al., *Spectrum of Mutations in BRCA 1, BRCA 2, CHEK and TP 53 in Families at High Risk of Breast Cancer*, 295 JAMA 1379 (2006). Using an alternative molecular testing method one study found that Myriad's test missed up to 12% of large genomic deletions or duplications, *id* at 1380, potentially causing grave harms.

Myriad's patents prevent laboratories from offering more rapid and cost effective methods, such as genomic capture and massive parallel sequencing for multiple breast and ovarian cancer susceptibility genes. King, *supra* at 4. If a result based upon the Myriad test is negative, testing for *other* breast or ovarian cancer genes are done selectively, costing thousands of dollars beyond the costs of Myriad's test. *Id.* With improved technology not used in Myriad's test, mutations can be identified in 21 known breast and ovarian cancer genes in one sample for less than $1500.00, and with further indexing and barcoding strategies, it can be done for less than $500.00 per sample. *Id.* Myriad's basic test is $3,300.00; its additional analysis test is $700.00.

Myriad's test is also less accurate than new methods, one of which evaluated multiple genes in addition to BRCA 1/2, identifying a wide range of mutations in a variety of genes. *Id.* Six large deletions and duplications were identified which could have been missed using Myriad's standard test. *Id.* Innovative new comprehensive parallel testing of multiple cancer susceptibility genes cannot be done on the BRCA 1/ 2 sequences without infringing Myriad's patents on isolated DNA.

Socio-economically disadvantaged women and women of ethnic and racial minorities are disproportionately harmed by Myriad's exclusive and broad patents. There is less access to genetic testing for underserved ethnic and racial minorities than for those in the white population. Armstrong K., Micco E., Carney A. et al, *Racial Differences in the Use of BRCA 1/2 Testing Among Women with a Family History of Breast or Ovarian Cancer,* 293 JAMA 1729 (2005). African-American women are 78% less likely to use genetic BRCA testing than white women, and although less diagnosed, they are more likely to die from the disease. *Id.*

The price of Myriad's standard test is necessarily prohibitive. Access to Myriad's test is severely limited for those without insurance, and even for the insured, the coverage for BRCA testing has been inconsistent and reimbursement is limited to those at high risk. *Report* at 37-38. The supplemental BART test is indicated for *all* patients with histories suggesting BRCA 1/2 mutations, however if a patient does not meet Myriad's defined criteria, the test is an additional $700.00. K.M. Shannon et al., *Which Individuals Undergoing BRCA Analysis Need BART Testing?* 204 Cancer Genetics 416 (2011). While some insurers reimburse the additional costs, others consider BART to be an investigational test, excluded from coverage. *Id.*

Myriad's patents also affect the quality of the tests for ethnic and racial minority women. Large genomic deletions or duplications, known as large genetic rearrangements will be found in approximately 12% of patients with both breast cancer and a "severe" family history who test negative for the BRCA genes. *Id.* Data from Myriad suggests that these large rearrangements BRCA mutations are over-represented and account for a larger percentage of mutations than previously thought in some populations, e.g., 20% of Latina women. *An Open Letter to Myriad Genetics,* Friday, July 22, 2011, *available at* http://yalecancergeneticcounseling.blogspot.com/2011_07_11 archive. html.

Lack of access to Myriad's tests for underserved racial and ethnic populations diminishes the quality of the test itself. Michael J. Hall, Olufunmilay I. Olopade, *Disparities in Genetic Testing: Thinking Outside the BRCA Box,* 24. J. Clin. Oncol. 2197 (2006). Models to assess risk used in BRCA testing need accurate estimates of the prevalence in specific populations to estimate probabilities in particularly high risk genotypes. *Id.* However the prevalence of Ashkenazi groups in testing shows a 10 fold increased prevalence in this group compared with estimates for the remaining U.S. population. *Id.* Without accurate estimates of mutation prevalence in minority subgroups, the reliability of these models is compromised. *Id.*

The preemption of the laws of nature, the embodied information of the BRCA 1/2 genes inhibits progress in biomedical research and treatment with serious and harmful implications for the health of women, particularly women who are underserved and socio-economically disadvantaged, as well as women of ethnic and racial minorities.

CONCLUSION

For the foregoing reasons, the petition for writ of certiorari should be granted.

Respectfully submitted,

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JOINT
APPENDIX

RECORD AND BRIEFS

No. 12-398

JAN 24 2013
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IN THE

Supreme Court of the United States

◆

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,

Petitioners,

—v.—

MYRIAD GENETICS, INC., ET AL.,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES
COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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PETITION FOR WRIT OF CERTIORARI FILED SEPTEMBER 25, 2012
PETITION FOR WRIT OF CERTIORARI GRANTED NOVEMBER 30, 2012

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09 Civ. 4515 (RWS)

RELEVANT DOCKET ENTRIES

NO.	DATE	DESCRIPTION
1	05/12/2009	COMPLAINT
25	07/13/2009	MOTION to Dismiss. Document filed by United States Patent and Trademark Office.
26	07/13/2009	MEMORANDUM OF LAW in Support re: 25 MOTION to Dismiss. Document filed by United States Patent and Trademark Office.
27	07/13/2009	MOTION to Dismiss. Document filed by Myriad Genetics.
28	07/13/2009	MEMORANDUM OF LAW in Support re: 27 MOTION to Dismiss. Document filed by Myriad Genetics.
29	07/13/2009	DECLARATION of Barry R. Satine in Support re: 27 MOTION to Dismiss. Document filed by Myriad Genetics.
34	08/26/2009	MEMORANDUM OF LAW in Opposition re: 25 MOTION to Dismiss.
35	08/26/2009	MEMORANDUM OF LAW in Opposition re: 27

		MOTION to Dismiss.
36	08/26/2009	DECLARATION of Daniel B. Ravicher in Opposition re: 27 MOTION to Dismiss. Document filed by American Society For Clinical Pathology
37	08/26/2009	DECLARATION of Mark Sobel in Opposition re: 27 MOTION to Dismiss.
38	08/26/2009	DECLARATION of Madhuri R. Hegde, Ph.D. in Opposition re: 27 MOTION to Dismiss.
39	08/26/2009	DECLARATION of Michael S. Watson, Ph.D. in Opposition re: 27 MOTION to Dismiss.
40	08/26/2009	DECLARATION of Wendy K. Chung, M.D., Ph.D. in Opposition re: 27 MOTION to Dismiss.
41	08/26/2009	DECLARATION of John R. Ball in Opposition re: 27 MOTION to Dismiss.
42	08/26/2009	DECLARATION of Roger A. Hubbard, Ph.D. in Opposition re: 27 MOTION to Dismiss.
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48	08/26/2009	DECLARATION of David H. Ledbetter, Ph.D. in Opposition re: 27 MOTION to Dismiss.
49	08/26/2009	DECLARATION of Ellen T. Matloff, M.S. in Opposition re: 27 MOTION to Dismiss.
50	08/26/2009	DECLARATION of Elsa W. Reich, M.S. in Opposition re: 27 MOTION to Dismiss.
51	08/26/2009	DECLARATION of Barbara A. Brenner in Opposition re: 27 MOTION to Dismiss.
52	08/26/2009	DECLARATION of Judy Norsigian in Opposition re: 27 MOTION to Dismiss.
53	08/26/2009	DECLARATION of Lisbeth Ceriani in Opposition re: 27 MOTION to Dismiss.

54	08/26/2009	DECLARATION of Runi Limary in Opposition re: 27 MOTION to Dismiss.
55	08/26/2009	DECLARATION of Genae Girard in Opposition re: 27 MOTION to Dismiss.
56	08/26/2009	DECLARATION of Patrice Fortune in Opposition re: 27 MOTION to Dismiss.
57	08/26/2009	DECLARATION of Vicky Thomason in Opposition re: 27 MOTION to Dismiss.
58	08/26/2009	DECLARATION of Kathleen Raker in Opposition re: 27 MOTION to Dismiss.
61	08/26/2009	MOTION for Summary Judgment
62	08/26/2009	MEMORANDUM OF LAW in Support re: 61 MOTION for Summary Judgment.
63	08/26/2009	RULE 56.1 STATEMENT.
64	08/26/2009	DECLARATION of Daniel B. Ravicher in Support re: 61 MOTION for Summary Judgment.
65	08/26/2009	DECLARATION of Daniel B. Ravicher in Support re: 61 MOTION for Summary Judgment.
66	08/26/2009	DECLARATION of Sir John E. Sulston, Ph.D. in Support re: 61 MOTION

		for Summary Judgment.
67	08/26/2009	DECLARATION of Wayne W. Grody, M.D., Ph.D. in Support re: 61 MOTION for Summary Judgment.
68	08/26/2009	DECLARATION of Debra G.B. Leonard, M.D., Ph.D. in Support re: 61 MOTION for Summary Judgment.
69	08/26/2009	DECLARATION of Christopher E. Mason, Ph.D. in Support re: 61 MOTION for Summary Judgment.
70	08/26/2009	DECLARATION of Myles W. Jackson, Ph.D. in Support re: 61 MOTION for Summary Judgment.
71	08/26/2009	DECLARATION of Elizabeth M. Swisher, M.D. in Support re: 61 MOTION for Summary Judgment.
72	08/26/2009	DECLARATION of Mildred K. Cho, Ph.D. in Support re: 61 MOTION for Summary Judgment.
73	08/26/2009	DECLARATION of Shobita Parthasarathy, Ph.D. in Support re: 61 MOTION for Summary Judgment.
74	08/26/2009	DECLARATION of Susan M. Love, M.D. in Support re: 61 MOTION for

		Summary Judgment.
75	08/26/2009	DECLARATION of Mark Sobel in Support re: 61 MOTION for Summary Judgment.
76	08/26/2009	DECLARATION of Madhuri R. Hegde, Ph.D. in Support re: 61 MOTION for Summary Judgment.
77	08/26/2009	DECLARATION of Michael S. Watson, Ph.D. in Support re: 61 MOTION for Summary Judgment.
78	08/26/2009	DECLARATION of Wendy K. Chung, M.D., Ph.D. in Support re: 61 MOTION for Summary Judgment.
79	08/26/2009	DECLARATION of John R. Ball in Support re: 61 MOTION for Summary Judgment. Document filed by American Society For Clinical Pathology, College of American Pathologists.
80	08/26/2009	DECLARATION of Roger A. Hubbard, Ph.D. in Support re: 61 MOTION for Summary Judgment.
81	08/26/2009	DECLARATION of John Scott in Support re: 61 MOTION for Summary Judgment.
82	08/26/2009	DECLARATION of Jeffrey A. Kant, M.D., Ph.D. in Support re: 61 MOTION

		for Summary Judgment.
83	08/26/2009	DECLARATION of Haig H. Kazazian, Jr., M.D. in Support re: 61 MOTION for Summary Judgment.
84	08/26/2009	DECLARATION of Arupa Ganguly, Ph.D. in Support re: 61 MOTION for Summary Judgment.
85	08/26/2009	DECLARATION of Harry Ostrer, M.D. in Support re: 61 MOTION for Summary Judgment.
86	08/26/2009	DECLARATION of David H. Ledbetter, Ph.D. in Support re: 61 MOTION for Summary Judgment.
87	08/26/2009	DECLARATION of Ellen T. Matloff, M.S. in Support re: 61 MOTION for Summary Judgment.
88	08/26/2009	DECLARATION of Elsa W. Reich, M.S. in Support re: 61 MOTION for Summary Judgment.
89	08/26/2009	DECLARATION of Barbara A. Brenner in Support re: 61 MOTION for Summary Judgment.
90	08/26/2009	DECLARATION of Judy Norsigian in Support re: 61 MOTION for Summary Judgment.
91	08/26/2009	DECLARATION of Lisbeth Ceriani in Support re: 61

		MOTION for Summary Judgment.
92	08/26/2009	DECLARATION of Runi Limary in Support re: 61 MOTION for Summary Judgment.
93	08/26/2009	DECLARATION of Genae Girard in Support re: 61 MOTION for Summary Judgment.
94	08/26/2009	DECLARATION of Patrice Fortune in Support re: 61 MOTION for Summary Judgment.
95	08/26/2009	DECLARATION of Vicky Thomason in Support re: 61 MOTION for Summary Judgment.
96	08/26/2009	DECLARATION of Kathleen Raker in Support re: 61 MOTION for Summary Judgment.
132	09/16/2009	MEMORANDUM OF LAW in Opposition re: 59 MOTION for Discovery. Document filed by Myriad Genetics.
135	09/23/2009	REPLY MEMORANDUM OF LAW in Support re: 25 MOTION to Dismiss. Document filed by United States Patent and Trademark Office.
136	09/23/2009	REPLY MEMORANDUM OF LAW in Support re: 59

		MOTION for Discovery.
137	09/23/2009	REPLY MEMORANDUM OF LAW in Support re: 27 MOTION to Dismiss. Document filed by Myriad Genetics.
138	09/23/2009	DECLARATION of Barry R. Satine in Support re: 27 MOTION to Dismiss. Document filed by Myriad Genetics.
140	11/02/2009	OPINION:# 98205 For the reasons stated above, Defendants' motion to dismiss the Complaint is denied.
142	11/20/2009	ANSWER to Complaint. Document filed by United States Patent and Trademark Office.
144	11/20/2009	ANSWER to Complaint. Document filed by Myriad Genetics.
152	12/23/2009	MOTION for Summary Judgment. Document filed by Myriad Genetics.
153	12/23/2009	MEMORANDUM OF LAW in Support IN SUPPORT OF THEIR MOTION FOR SUMMARY JUDGMENT AND (2) IN OPPOSITION TO PLAINTIFFS MOTION FOR SUMMARY JUDGMENT. Document filed by Myriad

		Genetics.
154	12/23/2009	RULE 56.1 STATEMENT. Document filed by Myriad Genetics.
155	12/23/2009	COUNTER STATEMENT TO 63 Rule 56.1 Statement. Document filed by Myriad Genetics.
156	12/23/2009	DECLARATION of Richard Baer in Support re: 61 MOTION for Summary Judgment. Document filed by Myriad Genetics.
157	12/23/2009	DECLARATION of Melanie K. Bone in Support re: 61 MOTION for Summary Judgment. Document filed by Myriad Genetics.
158	12/23/2009	DECLARATION of Dr. Gregory C. Critchfield in Support re: 61 MOTION for Summary Judgment, Document filed by Myriad Genetics.
159	12/23/2009	DECLARATION of John J. Doll in Support re: 61 MOTION for Summary Judgment. Document filed by Myriad Genetics.
160	12/23/2009	DECLARATION of Richard P. Frieder, MD in Support re: 61 MOTION for Summary Judgment.

		Document filed by Myriad Genetics.
161	12/23/2009	DECLARATION of DR. MARK A. KAY in Support re: 61 MOTION for Summary Judgment. Document filed by Myriad Genetics.
162	12/23/2009	DECLARATION of Jenny Lessman in Support re: 61 MOTION for Summary Judgment. Document filed by Myriad Genetics.
163	12/23/2009	DECLARATION of RONG LI, PhD in Support re: 61 MOTION for Summary Judgment. Document filed by Myriad Genetics.
164	12/23/2009	DECLARATION of Nancy J. Linck in Support re: 61 MOTION for Summary Judgment. Document filed by Myriad Genetics.
165	12/23/2009	DECLARATION of TODD OGAARD in Support re: 61 MOTION for Summary Judgment. Document filed by Myriad Genetics.
166	12/23/2009	DECLARATION of Jeffrey D. Parvin in Support re: 61 MOTION for Summary Judgment. Document filed by Michael K. Young.
167	12/23/2009	DECLARATION of DR. PHILIP R. REILLY in

		Support re: 61 MOTION for Summary Judgment. Document filed by Myriad Genetics.
168	12/23/2009	DECLARATION of WILLIAM E. RUSCONI in Support re: 61 MOTION for Summary Judgment. Document filed by Myriad Genetics.
169	12/23/2009	DECLARATION of Dr. John Franklin Sandbach in Support re: 61 MOTION for Summary Judgment. Document filed by Myriad Genetics.
170	12/23/2009	DECLARATION of JOSEPH SCHLESSINGER. PH.D. in Support re: 61 MOTION for Summary Judgment. Document filed by Myriad Genetics.
171	12/23/2009	DECLARATION of Dr. Donna Shattuck in Support re: 61 MOTION for Summary Judgment. Document filed by Myriad Genetics.
172	12/23/2009	DECLARATION of DR. MARK SKOLNICK in Support re: 61 MOTION for Summary Judgment. Document filed by Myriad Genetics.

173	12/23/2009	DECLARATION of JOSEPH STRAUS in Support re: 61 MOTION for Summary Judgment. Document filed by Myriad Genetics.
174	12/24/2009	DECLARATION of DR. SEAN TAVTIGIAN in Support re: 61 MOTION for Summary Judgment. Document filed by Myriad Genetics.
175	12/24/2009	MOTION for Judgment on the Pleadings. Document filed by United States Patent and Trademark Office.
176	12/24/2009	MEMORANDUM OF LAW in Support re: 175 MOTION for Judgment on the Pleadings. Document filed by United States Patent and Trademark Office.
177	12/24/2009	COUNTER STATEMENT TO 63 Rule 56.1 Statement. Document filed by United States Patent and Trademark Office.
219	01/20/2010	FIRST MEMORANDUM OF LAW in Opposition re: 175 MOTION for Judgment on the Pleadings, 152 MOTION

		for Summary Judgment. And in support of 61 Plaintiffs' Motion for Summary Judgment.
220	01/20/2010	COUNTER STATEMENT TO 154 Rule 56.1 Statement.
221	01/20/2010	DECLARATION of Robert L. Nussbaum, M.D. in Opposition re: 175 MOTION for Judgment on the Pleadings, 152 MOTION for Summary Judgment.
222	01/20/2010	DECLARATION of Christopher E. Mason, Ph.D. in Opposition re: 175 MOTION for Judgment on the Pleadings, 152 MOTION for Summary Judgment.
223	01/20/2010	DECLARATION of Roger D. Klein, M.D., J.D. in Opposition re: 175 MOTION for Judgment on the Pleadings, 152 MOTION for Summary Judgment.
224	01/20/2010	DECLARATION of Joseph E. Stiglitz, Ph.D. in Opposition re: 175 MOTION for Judgment on the Pleadings, 152 MOTION for Summary Judgment.

225	01/20/2010	DECLARATION of Fiona E. Murray, Ph.D. in Opposition re: 175 MOTION for Judgment on the Pleadings, 152 MOTION for Summary Judgment.
226	01/20/2010	DECLARATION of Thomas B. Kepler in Opposition re: 175 MOTION for Judgment on the Pleadings, 152 MOTION for Summary Judgment.
227	01/20/2010	DECLARATION of Robert Cook-Deegan in Opposition re: 175 MOTION for Judgment on the Pleadings, 152 MOTION for Summary Judgment.
228	01/20/2010	DECLARATION of Ellen T. Matloff, MS in Opposition re: 175 MOTION for Judgment on the Pleadings, 152 MOTION for Summary Judgment.
244	01/29/2010	REPLY MEMORANDUM OF LAW in Support re: 152 MOTION for Summary Judgment. Document filed by Myriad Genetics.
245	01/29/2010	REPLY MEMORANDUM OF LAW in Support re:

		175 MOTION for Judgment on the Pleadings. Document filed by United States Patent and Trademark Office.
246	01/29/2010	DECLARATION of LAURA A. CORUZZI in Support re: 152 MOTION for Summary Judgment. Document filed by Myriad Genetics.
255	03/29/2010	OPINION #98799 re: 175 For the reasons set forth in this Opinion, Plaintiffs' motion for summary judgment is granted in part, Myriad's motion for summary judgment is denied, the USPTO's motion for judgment on the pleadings is granted, and the claims-in-suit are declared invalid pursuant to 35 U.S.C. 101. Submit judgment on notice. It is so ordered. (Signed by Judge Robert W. Sweet on 3/29/2010) (tro) Modified on 4/7/2010.
256	04/05/2010	AMENDED OPINION: #98799 For the reasons set forth above, Plaintiffs' motion for summary judgment is granted in part, Myriad's motion for

		summary judgment is denied, the USPTO's motion for judgment on the pleadings is granted, and the claims-in-suit are declared invalid pursuant to 35 U.S.C. § 101. Submit judgment on notice. (Signed by Judge Robert W. Sweet on 4/2/2010) (jpo) Modified on 4/5/2010 (ml). Modified on 4/7/2010.
258	04/19/2010	JUDGMENT granting plaintiffs' motion for summary judgment in part, granting defendant USPTO's motion for judgment on the pleadings, and denying the Myriad Defendants' motion for summary judgment. (Signed by Judge Robert W. Sweet on 4/19/10) (Attachments: # 1 NOTICE OF RIGHT TO APPEAL)(ml)
259	06/16/2010	NOTICE OF APPEAL TO THE FEDERAL CIRCUIT from 258 Judgment. Document filed by Myriad Genetics.

IN THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

No. 2010-1406

RELEVANT DOCKET ENTRIES

No.	**Date**	**Description**
39	10/22/2010	Brief for the Appellants (With Separately Bound Addendum). BY Myriad Genetics, Inc. (Appellant).
70	10/29/2010	Brief for the United States as Amicus Curiae in Support of Neither Party. BY United States (Amicus).
156	11/30/2010	Brief for The Appellees. BY The Association for Molecular Pathology, et al. (Appellees).
204	12/22/2010	Reply Brief for the Appellants. BY Arnold B. Combe, Director, University of Utah Research Foundation, et al. (Appellants).
205	12/29/2010	Appendix (Seven Volumes). BY Myriad Genetics, Inc., et al. (Appellants).
206	01/04/2011	Appellants Myriad Genetics, et al's Citation of Supplemental Authority pursuant to Rule 28(j). (merits panel)
246	03/08/2011	By Amicus - Unopposed Motion of Amicus Curiae The United States for Leave to Participate in Oral Argument and for Enlargement of Argument time.
257	03/30/2011	Second Corrected Appendix

		Volume III and VI. BY Myriad Genetics, Inc., et al. (Appellants).
261	07/27/2011	Appellants Myriad Genetics, Inc., et al.'s letter to Court regarding April 4 oral argument concerning jurisdictional issues.
262	07/29/2011	Opinion
263	08/26/2011	Appellees [The Association for Molecular Pathology, et al.]-Petition for Rehearing.
264	08/29/2011	Appellants [Myriad Genetics, Inc., et al.]-Petition for Rehearing. Response requested from: Appellees (The Association for Molecular Pathology). Response filed: 9/15/2011
265	08/31/2011	Letter (dated 7/29/2011) from C. Hansen, principal attorney for appellees, regarding Dr. Ostrer leaving NYU.
266	09/09/2011	Letter of Gregory A. Castanias, principal attorney for appellants, clarifying two citations in appellants' petition for rehearing
267	09/13/2011	Petition Action: Denied on 9/13/2011.
268	09/16/2011	Petition Action: Denied on 9/16/2011.
272	03/26/2012	Notice from Clerk of Supreme Court of United States that the petition for writ of certiorari

		was granted on 3/26/2012. Judgment is vacated. Case is remanded to Federal Circuit for further consid. in light of Mayo Collaborative v. Prometheus Labs.
283	05/30/2012	By Appellants Appellants' Suggestion of Mootness, or, in the Alternative, Motion to Remand
288	06/08/2012	Reply 1 re: entry #283 Appellants' Suggestion of Mootness, or, in the Alternative, Motion to Remand
293	06/11/2012	The court declines the suggestion and denies the motion.
303	06/14/2012	Supplemental Brief for Appellees The Association for Molecular Pathology, et al. BY The Association for Molecular Pathology, et al. (Appellees).
320	06/15/2012	Supplemental Brief for Appellants, Myriad Genetics, Lorris Betz, Roger Boyer, et al. BY Myriad Genetics, Inc., et al. (Appellants).
331	06/15/2012	Brief for The United States as Amicus Curiae in support of neither party. BY United States (Amicus).
394	06/29/2010	By Amicus United States-Motion for Leave to Participate in Oral argument and for extension of argument time.

395	07/03/2012	Granted in part. The argument time is expanded to provide for 10 min. for appellees, 10 minutes for the government, and 20 minutes for Myriad.
406	08/16/2012	Opinion
415	11/30/2012	Notice from the Clerk of the Supreme Court of the United States that the petition for a writ of certiorari was granted limited to Question 1 presented by the petition on November 30, 2012.

[Complaint, filed May 12, 2009]

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

09 Civ. 4515 (RWS)

ASSOCIATION FOR MOLECULAR PATHOLOGY; AMERICAN COLLEGE OF MEDICAL GENETICS; AMERICAN SOCIETY FOR CLINICAL PATHOLOGY; COLLEGE OF AMERICAN PATHOLOGISTS; HAIG KAZAZIAN, MD; ARUPA GANGULY, PhD; WENDY CHUNG, MD, PhD; HARRY OSTRER, MD; DAVID LEDBETTER, PhD; STEPHEN WARREN, PhD; ELLEN MATLOFF, M.S.; ELSA REICH, M.S.; BREAST CANCER ACTION; BOSTON WOMEN'S HEALTH BOOK COLLECTIVE; LISBETH CERIANI; RUNI LIMARY; GENAE GIRARD; PATRICE FORTUNE; VICKY THOMASON; KATHLEEN RAKER,

Plaintiffs,

v.

UNITED STATES PATENT AND TRADEMARK OFFICE; MYRIAD GENETICS; LORRIS BETZ, ROGER BOYER, JACK BRITTAIN, ARNOLD B. COMBE, RAYMOND GESTELAND, JAMES U. JENSEN, JOHN KENDALL MORRIS, THOMAS PARKS, DAVID W. PERSHING, and MICHAEL K. YOUNG, in their official capacity as Directors of the University of Utah Research Foundation,

Defendants.

INTRODUCTION

1. Every person's body contains human genes, passed down to each individual from his or her parents. These genes determine, in part, the structure and function of every human body. This case challenges the legality and constitutionality of granting patents over this most basic element of every person's individuality.

2. The gene patents that are challenged in this case are patents covering the *BRCA*1 and *BRCA*2 genes, which relate to an increased risk of breast and/or ovarian cancer. Ease of access to genomic discoveries is crucial if basic research is to be expeditiously translated into clinical laboratory tests that benefit patients in the emerging era of personalized and predictive medicine. The patents make ease of access more restricted. Because of the patents, defendant Myriad has the right to prevent clinicians from independently looking at or interpreting a person's *BRCA*1 and *BRCA*2 genes to determine if the person is at a higher risk of breast and/or ovarian cancer. Because of the patents and because Myriad chooses not to license the patents broadly, women who fear they may be at an increased risk of breast and/or ovarian cancer are barred from having anyone look at their *BRCA*1 and *BRCA*2 genes or interpret them except for the patent holder. Women are thereby prevented from obtaining information about their health risks from anyone other than the patent holder, whether as an initial matter or to obtain a second opinion. The patents also prevent doctors or laboratories from independently offering testing to their patients, externally validating the test, or working

cooperatively to improve testing. Many women at risk cannot even be tested because they are uninsured and/or cannot afford the test offered by Myriad.

3. The patents cover the human genes themselves. In this respect, they cover the healthy gene and numerous variations of the gene, some of which Myriad identified, some of which it did not, and some of which have not yet been identified. Some of those variations correlate with an increased risk of breast and ovarian cancer. Some do not. The patents also cover any new methods of looking at the human genes that might be developed by others, the concept of comparing one *BRCA*1 or *BRCA*2 gene to another *BRCA*1 or *BRCA*2 gene for the purpose of discerning differences, and the correlations found in nature between mutations in the human gene and an increased risk of breast or ovarian cancer.

4. The patenting of human genes, the concept of looking at or comparing human genes, and correlations found in nature between certain genes and an increased risk of breast and/or ovarian cancer violates long established legal principles that prohibit the patenting of laws of nature, products of nature, and abstract ideas. These patents also violate the First Amendment and Article I, section 8, clause 8 of the United States Constitution.

JURISDICTION AND VENUE

5. This Court has jurisdiction pursuant to 28 U.S.C. §§ 1331, 1338(a), and 2201. Litigation is authorized by 42 U.S.C. §1983.

6. Venue is proper pursuant to 28 U.S.C. § 1391(b)(1) and (2), (c) and (e).

PARTIES

7. Plaintiff ASSOCIATION FOR MOLECULAR PATHOLOGY (AMP) is a not-for-profit scientific society dedicated to the advancement, practice, and science of clinical molecular laboratory medicine and translational research based on the applications of genomics and proteomics. AMP members participate in basic and translational research aimed at broadening the understanding of gene/protein structure and function, disease processes, and molecular diagnostics, and provide clinical medical services for patients, including diagnosis of breast cancer. AMP supports attaching intellectual property rights to true acts of invention such as new therapeutics, diagnostics or technology platforms, but believes a single gene or a sequence of the genome is a product of nature and should not be patentable. AMP sues on behalf of its members, some of whom are ready, willing, and able to engage in research and clinical practice involving the *BRCA*1 and *BRCA*2 genes if the patents are invalidated.

8. Plaintiff AMERICAN COLLEGE OF MEDICAL GENETICS (ACMG) is a private, non-profit voluntary organization of clinical and laboratory geneticists. The Fellows of the ACMG are doctoral level medical geneticists and other physicians involved in the practice of medical genetics. With more than 1300 members, the ACMG's mission is to improve health through the practice of Medical Genetics. In order to fulfill this mission, the ACMG strives to 1) define and promote excellence in medical genetics practice and the integration of translational research into practice; 2) promote and provide medical genetics education; 3)

increase access to medical genetics services and integrate genetics into patient care; and 4) advocate for and represent providers of medical genetics services and their patients. ACMG sues on behalf of its members, some of whom are ready, willing, and able to engage in research and clinical practice involving the *BRCA*1 and *BRCA*2 genes if the patents are invalidated.

9. Founded in 1922, the plaintiff AMERICAN SOCIETY FOR CLINICAL PATHOLOGY (ASCP) is the largest and oldest organization representing the medical specialty of pathology and laboratory medicine. The ASCP has 130,000 members working as pathologists and laboratory professionals. ASCP members design and interpret the tests that detect disease, predict outcome, and determine the appropriate therapy for the patient. The ASCP is recognized for its excellence in continuing professional education, certification of laboratory professionals, and advocacy--championing causes at the state and federal levels. ASCP is a not-for-profit entity organized for scientific and educational purposes and dedicated to patient safety, public health, and the practice of pathology and laboratory medicine. ASCP sues on behalf of its members, some of whom are ready, willing, and able to engage in research and clinical practice involving the *BRCA*1 and *BRCA*2 genes if the patents are invalidated.

10. Plaintiff COLLEGE OF AMERICAN PATHOLOGISTS (CAP) is a national medical society representing more than 17,000 pathologists who practice anatomic pathology and laboratory medicine in laboratories worldwide. The College's Commission on Laboratory Accreditation is responsible for

accrediting more than 6,000 laboratories domestically and abroad and approximately 23,000 laboratories are enrolled in CAP's proficiency testing programs, It is the world's largest association composed exclusively of board-certified pathologists and pathologists in training worldwide and is widely considered the leader in laboratory quality assurance. The CAP is an advocate for high-quality and cost-effective medical care. CAP sues on behalf of its members, some of whom are ready, willing, and able to engage in research and clinical practice involving the *BRCA*1 and *BRCA*2 genes if the patents are invalidated.

11. Plaintiff HAIG KAZAZIAN, MD, is the Seymour Gray Professor of Molecular Medicine in Genetics in the Department of Genetics at the University of Pennsylvania School of Medicine. He is a human genetics researcher and the previous chair of the Department. Dr. Kazazian received a cease and desist letter from defendant Myriad as a result of work that was being done in the Genetic Diagnostic Laboratory of the Department of Genetics. The laboratory directed by Dr. Kazazian was and is prohibited from doing routine screening for *BRCA*1 and *BRCA*2 genes for research or part of clinical practice without Myriad's permission as a direct result of the patents challenged by this action.

12. Plaintiff ARUPA GANGULY, PhD, is an Associate Professor in the Department of Genetics at the Hospital of the University of Pennsylvania. Dr. Ganguly was engaged in research on and clinical practice relating to breast cancer. Dr. Kazazian received a cease-and-desist letter from defendant Myriad. Dr. Ganguly, the co-director of the

laboratory was ready, willing, and able to resume research and clinical practice if the patents had been invalidated. If they are invalidated now, she would seriously consider resuming clinical practice that is now prohibited.

13. Plaintiff WENDY CHUNG, MD, PhD, is an Associate Professor of Pediatrics at Columbia University. Dr. Chung is a human geneticist whose current research includes research on the *BRCA*1 and *BRCA*2 genes. Dr. Chung is required to send samples to defendant Myriad for any analysis of the *BRCA*1 or *BRCA*2 genes if she wants to tell the subjects the results and use the results clinically. Dr. Chung could evaluate the samples herself, or find other laboratories to evaluate the samples, if the patents are invalidated. She is ready, willing, and able to do so if the patents are invalidated.

14. Plaintiff HARRY OSTRER, MD, is a Professor of Pediatrics, Pathology and Medicine and Director of the Human Genetics Program in the Department of Pediatrics at New York University School of Medicine. Dr. Ostrer's work has focused on understanding the genetic basis of development and disease, including disorders of sexual differentiation and genetic susceptibility to breast and prostate cancer and malignant melanoma. Dr. Ostrer is actively engaged in identifying genes that convey risk of breast cancer and that may mitigate the effects of mutations in the BRCA1 and BRCA2 genes. These observations could infringe on the Myriad patents and, thus, could be prevented from entering clinical practice and benefitting people. Dr. Ostrer is also the Director of the Molecular Genetics Laboratory of NYU Medical Center, one of the largest

academic genetic testing laboratories in the United States. His laboratory has the ability to evaluate *BRCA*1 and *BRCA*2 genes in samples, including in custom-designed tests that may be more cost-effective than Myriad's current offering. Dr. Ostrer could evaluate the samples himself, or find other laboratories to evaluate the samples, if the patents are invalidated. He is ready, willing, and able to do so if the patents are invalidated.

15. Plaintiff DAVID LEDBETTER, PhD, is a Professor of Human Genetics and Director of the Division of Medical Genetics at the Emory University School of Medicine. Dr. Ledbetter is a genetic researcher. Research in his laboratory focuses on the molecular characterization of human developmental disorders. Dr. Ledbetter directs the Emory Genetics Laboratory which provides superior testing services for individuals with or at risk for genetic diseases. Dr. Ledbetter's laboratory has the ability to evaluate *BRCA*1 and *BRCA*2 genes in samples. Dr. Ledbetter could evaluate the samples himself, or find other laboratories to evaluate the samples, if the patents are invalidated. He is ready, willing, and able to do so if the patents are invalidated.

16. Plaintiff STEPHEN T. WARREN, PhD, is the William Patterson Timmie Professor of Human Genetics, Chairman of the Department of Human Genetics, and Professor of Biochemistry and Professor of Pediatrics at Emory University. He is a past President of the American Society of Human Genetics. He personally supervises genetic research at Emory. He is also responsible for the laboratories at the Emory Genetics Laboratory. The laboratory has the ability to evaluate *BRCA*1 and *BRCA*2 genes

in samples. Scientists at Emory could evaluate the samples themselves, or find other laboratories to evaluate the samples, if the patents are invalidated. Dr. Warren is ready, willing, and able to do so if the patents are invalidated.

17. Plaintiff ELLEN MATLOFF, MS, is Director of the Yale Cancer Genetic Counseling Program. Ms. Matloff advises women on the desirability of obtaining an analysis of their genes to determine if the women have the genetic mutations that correlate with an increased risk of breast and/or ovarian cancer. If she determines that such an analysis is warranted and the individual woman concurs, Ms. Matloff arranges for the analysis and then advises the woman of the significance of the results. Ms. Matloff currently is forced to utilize defendant Myriad for analysis of the *BRCA*1 and *BRCA*2 genes. If the patents were invalidated, she would utilize other laboratories and other methods of analysis, some of which she believes could be offered at a substantially reduced cost. She is ready, willing, and able to utilize those additional resources if the patents are invalidated.

18. Plaintiff ELSA W. REICH, M.S. is a Professor in the Department of Pediatrics at New York University. She is a genetic counselor. She helps women decide whether to be tested for mutations in the *BRCA*1 and *BRCA*2 genes. If they need testing, she sends samples to defendant Myriad and interprets the results for the women. Having only one laboratory prevents independent confirmation of test results and interpretation of the meaning of variants of uncertain significance. She is ready,

willing, and able to utilize alternative testing facilities for such tests if the patents are invalidated.

19. Plaintiff BREAST CANCER ACTION is a national organization of over 20,000 members based in San Francisco, California. Founded in 1990, Breast Cancer Action was started by women in a San Francisco breast cancer support group who were frustrated by the lack of knowledge about their disease. Their goal was to create an organization that would help transform breast cancer from a private medical crisis to a public health emergency. Breast Cancer Action continues this work, and is now a national education and activist organization that challenges assumptions and inspires change to end the breast cancer epidemic. The organization works with researchers to encourage innovative approaches to unresolved issues in breast cancer, including issues raised by research on the *BRCA*1 and *BRCA*2 genes that is not currently being done. Members of Breast Cancer Action have had their *BRCA*1/*BRCA*2 genes analyzed or sought analysis to determine if they have genetic mutations that correlate with an increased risk of breast and/or ovarian cancer. In addition, Breast Cancer Action staff and volunteers provide information to members of the public about genetic analysis. If the patents are invalidated, Breast Cancer Action and its members are ready, willing, and able to utilize any additional resources for such analysis, and would directly benefit from any increased research on the *BRCA*1 and *BRCA*2 genes that would be made possible. Breast Cancer Action would also be able to provide information about testing options offered by labs other than Myriad without fear of inducing infringement.

Breast Cancer Action sues on behalf of itself and its members.

20. Plaintiff BOSTON WOMEN'S HEALTH BOOK COLLECTIVE (BWHBC), doing business as Our Bodies Ourselves, is a nonprofit, public interest women's health education, advocacy, and consulting organization. OBOS provides clear, accurate information about health, sexuality and reproduction from a feminist and consumer perspective. OBOS vigorously advocates for women's health by challenging the institutions and systems that block women from full control over their bodies and devalue women's lives. OBOS's long-standing commitment to serve only in the public interest and its bridge-building capacity are its hallmarks. In addition, OBOS staff provide information to members of the public about genetic analysis. If the patents are invalidated, OBOS is ready, willing, and able to provide information about testing options offered by labs other than Myriad without fear of inducing infringement, and would directly benefit from any increased research on the *BRCA*1 and *BRCA*2 genes that would be made possible.

21. Plaintiff LISBETH CERIANI is a 43-year-old single mother who was diagnosed with cancer in both breasts in May 2008. Ms. Ceriani is insured through MassHealth, a Medicaid insurance program for low-income people. Her oncologist and genetic counselor recommended that she obtain *BRCA*1 and *BRCA*2 genetic testing, because she may need to consider further surgery in order to reduce her risk of ovarian cancer. They submitted a blood sample to Myriad on her behalf. However, she was notified that Myriad would not process the sample. Even though her

insurance has informed her that it would cover the BRCA genetic test. Myriad will not accept the MassHealth coverage. Ms. Ceriani is unable to pay the full cost out-of-pocket and, to date, has not been tested. Without the genetic test results, she cannot determine the best medical course for herself. If the patents are invalidated, Ms. Ceriani is ready, willing, and able to utilize any additional resources for testing and research.

22. Plaintiff RUNI LIMARY is a 32-year-old Asian-American woman who was diagnosed with aggressive breast cancer in 2005. Upon her diagnosis, she sought *BRCA* genetic testing, but her insurance company did not cover the test. Ms. Limary was not able to get tested through Myriad until two years later, when she obtained insurance that provided coverage for the test. Ms. Limary was given the following test result: "genetic variant of uncertain significance." The test she received did not look for all known large rearrangements in the BRCA genes. Ms. Limary wants to access additional resources for testing and research that could reveal the significance of the variant in her genes, including whether the variant is correlated with an increased risk of breast or ovarian cancer. If the patents are invalidated, Ms. Limary is ready, willing, and able to utilize any additional resources for testing and research.

23. Plaintiff GENAE GIRARD is a 39-year-old woman who was diagnosed with breast cancer in 2006. Shortly after her diagnosis, she obtained *BRCA*1/*BRCA*2 genetic testing from Myriad and tested positive for a deleterious mutation on the *BRCA*2 gene. She sought a second opinion of that

test result but learned that Myriad is the only laboratory in the country that can provide full sequencing. The patents on the *BRCA* genes block her from getting confirmation of the test she received. Ms. Girard has been forced to make, and continues to make, significant medical decisions for herself based on a test result that has not been verified by another laboratory. A second opinion on Ms. Girard's test results is also crucial for her immediate family's options and screening. If the patents are invalidated, Ms. Girard is ready, willing, and able to utilize any additional resources for testing and research.

24. Plaintiff PATRICE FORTUNE is a 48-year-old woman who was diagnosed with breast cancer in February 2009. Ms. Fortune is insured through Medi-Cal, a Medicaid insurance program for low-income people. Her oncologist and genetic counselor recommended that she obtain *BRCA1*/*BRCA2* genetic testing, including the supplemental testing that is offered by Myriad separate from its standard test, but told her that Myriad would not accept her insurance. Ms. Fortune is unable to pay the full cost out-of-pocket and, to date, has not been tested. Without the genetic test results, she cannot determine the best medical course for herself. If the patents are invalidated, Ms. Fortune is ready, willing, and able to utilize any additional resources for testing and research.

25. Plaintiff VICKY THOMASON is a 52-year-old woman who was diagnosed with ovarian cancer in 2006. She obtained *BRCA1*/*BRCA2* genetic testing from Myriad in 2007 and was found to be negative for mutations covered by that test. Her genetic

counselor advised her about additional *BRCA* genetic testing that looks for other large genetic rearrangements that are not included in Myriad's standard full sequencing test, but informed her that her insurance would not cover the full cost of that test. Upon information and belief, Ms. Thomason would need to pay up front for this additional test. Ms. Thomason is unable to afford the extra cost and, to date, has not received this testing. Without these results, she cannot determine the best medical course for herself. If the patents are invalidated, Ms. Thomason is ready, willing, and able to utilize any additional resources for testing and research that would become accessible to her.

26. Plaintiff KATHLEEN RAKER is a 41-year-old woman whose mother and maternal grandmother died from breast cancer. She obtained *BRCA1*/*BRCA2* genetic testing from Myriad in 2007 and was found to be negative for mutations covered by that test. Her genetic counselor advised her about additional *BRCA* genetic testing that looks for other large genetic rearrangements that are not included in Myriad's standard full sequencing test, but informed her that it was unclear whether her insurance would cover the cost of that test. Upon information and belief, Ms. Raker would need to pay up front for this additional test. Ms. Raker is unable to afford the extra cost and, to date, has not received this testing. Without these results, she cannot determine the best medical course for herself. If the patents are invalidated, Ms. Raker is ready, willing, and able to utilize any additional resources for testing and research that would become accessible to her.

27. Defendant UNITED STATES PATENT AND TRADEMARK OFFICE (Patent office) is an agency of the Commerce Department of the United States. Its principal office is in Alexandria, Virginia. The Patent office is sued solely on the constitutional claims.

28. Defendant MYRIAD GENETICS (Myriad) is a for–profit corporation located in Salt Lake City, Utah and doing business throughout the United States. Myriad is incorporated in Delaware. Myriad is a co-owner of patent 5,747,282, and formerly was a co-owner of several of the other patents challenged in this lawsuit. Upon information and belief, Myriad now has an exclusive license for all of the patents challenged in this action and is the sole clinical provider of full sequencing of the *BRCA*1 and *BRCA*2 genes in the United States.

29. Defendants LORRIS BETZ, ROGER BOYER, JACK BRITTAIN, ARNOLD B. COMBE, RAYMOND GESTELAND, JAMES U. JENSEN, JOHN KENDALL MORRIS, THOMAS PARKS, DAVID W. PERSHING, and MICHAEL K. YOUNG are Directors of the University of Utah Research Foundation. The foundation is a not-for-profit corporation that is operated, supervised and/or controlled by the University of Utah and located in Salt Lake City, Utah. The University of Utah Research Foundation is an owner or part-owner of all of the patents at issue in this case. Because Myriad holds the exclusive license to these patents, defendant patent-holders, including Myriad and the University of Utah Research Foundation, are hereafter referred to collectively as Myriad.

30. The United States of America, represented by the Secretary of Health and Human Services, is an additional owner of the patents 5,710,001, 5,753,441, 6,162,897 and 5,747,282. Endo Recherche, Inc., of Quebec, Canada, HSC Research and Development Limited Partnership of Toronto, Canada, and the Trustees of the University of Pennsylvania are additional owners of the patents 5,837,492 and 6,033,857. These other owners have not been joined as parties because their participation is unnecessary to the resolution of this action, and Myriad, as the exclusive licensee of all of the patents, is fully capable of representing the interests of all of the patent owners.

FACTS

31. Defendant U.S. Patent Office has granted, and Myriad holds, either through ownership or exclusive license, numerous patents relating to the human genes known as *BRCA*1 and *BRCA*2.

32. Plaintiffs challenge the legality and the constitutionality of four categories of claims in these patents:

a. Patent Claims Over Natural Human Genes: Claims 1, 2, 5, and 6 of patent 5,747,282 ('282) and claim 1 of patent 5,837,492 ('492).

b. Patent Claims Over Natural Human Genes With Natural Mutations: Claim 1 of patent 5,693,473 ('473), claim 7 of patent '282, and claims 6 and 7 of patent '492.

c. Patent Claims Over Any Method, Including Non-Patented Methods, Of Looking For

Mutations in Natural Human Genes: Claim 1 of patent 5,709,999 ('999).

d. Patent Claims Over The Thought That Two Genes Are Different or Have Different Effects, Including But Not Limited To The Thought That The Differences Correlate With An Increased Risk Of Breast And/Or Ovarian Cancer: Claim 1 of patent 5,710,001 ('001), claim 1 of patent 5,753,441 ('441), claims 1 and 2 of patent 6,033,857 ('857) and claim 20 of patent '282.

33. Every person's body is composed of cells. In the nucleus of each cell is the person's DNA. Genes are encoded by DNA. Genes instruct the body to create the proteins and gene products that that person's body uses to function. Human DNA and human genes consist of hundreds or thousands of nucleotides (i.e. bases) referred to as A, T, G, and C. A gene is represented in scientific research and the patents in this case, by the genomic sequence, the series of nucleotides (represented by the letters) corresponding to the bases.

34. DNA is a chemical structure made by the body. However, the genetic sequence is informational both for clinicians and researchers and for the body itself.

35. Not everyone's DNA or genes are identical. Genes vary in nature from one person to another and those variations are often called mutations or variants. Those variants can include such changes as a T appearing where an A normally appears or a G being deleted from the DNA sequence. Variants can be inherited and can also be acquired during a

lifetime. They can also include much larger variations such as sections of DNA that are missing or displaced. Some of these variants have effects on the body's ability to create proteins necessary for sound health.

36. To find out if a person has a T where an A normally appears, a genetic researcher or clinician looks at the sequence of an individual's gene. The researcher or clinician can sequence that gene -- i.e. read the A, T, C, G letters of the gene. Once the sequence is known, the researcher or clinician can look at it to see if the letters show a healthy sequence, a sequence with mutations known to be associated with cancer, or a sequence with one or more variants of uncertain significance. Alternatively, the researcher or clinician can check just a small section of the sequence where a known mutation or variant is known to occur. The methods by which researchers or clinicians identify the sequence of either the whole gene or any part thereof are not patented in the claims at issue here and are well known in the field.

37. The genes covered by the patents in this case are called *BRCA*1 and *BRCA*2 because of their association with breast cancer. Every man and woman has *BRCA*1 and *BRCA*2 genes, but the genomic sequence of each person's *BRCA* genes can differ. Certain mutations in the genes are correlated with an increased risk of breast and/or ovarian cancer. Scientists also have found that mutations in these genes may be associated with other cancers, such as prostate and pancreatic cancers.

38. Breast cancer is one of the leading causes of death among women. Approximately 5-10% of the

women who develop breast cancer are likely to have a mutation, inherited from one of their parents, in their *BRCA*1 or *BRCA*2 genes, that predisposes them to an increased risk of breast and/or ovarian cancer.

39. Women with one of these significant gene mutations in the *BRCA*1 or *BRCA*2 gene have an approximately 40-85% lifetime risk of developing breast cancer. Inherited mutations on the *BRCA*1 and *BRCA*2 genes also increase the risk of ovarian cancer.

40. A *BRCA*1/*BRCA*2 genetic test result that is positive for one of these mutations can have a substantial impact on a woman's medical decisions and health. It can also have an impact on that woman's relatives. Many women will obtain earlier and more vigilant screening for breast and/or ovarian cancers, and some women may choose to have prophylactic surgery to remove their breasts and/or ovaries in order to reduce the risk of future cancers.

41. In the 1990's, a number of genetic researchers around the world began looking for a human gene that correlated with an increased risk of breast and/or ovarian cancer. Many of those researchers, including the researchers who ultimately formed defendant Myriad, were funded, at least in part, by the federal government.

42. Researchers, using techniques widely available in the profession, determined in 1990 that one gene that correlated with an increased risk of breast and/or ovarian cancer was located in the body on chromosome 17.

43. Another researcher team, eventually associated with defendant Myriad, also using

techniques widely available in the profession. sequenced the precise *BRCA*1 gene. They subsequently formed Myriad. They sought, and ultimately obtained, several patents on this human *BRCA*1 gene.

44. Scientists knew that *BRCA*1 was not the only gene that predisposed women to an increased risk of inherited breast and/or ovarian cancer. Researchers from all over the world began looking for other similar genes, again using techniques widely available in the profession.

45. Defendant Myriad, using techniques widely available in the profession, filed patents over the *BRCA*2 gene. Myriad ultimately obtained a series of patents over the human *BRCA*2 gene.

46. Defendant Myriad did not invent, create or in any way construct or engineer the human *BRCA*1 and *BRCA* 2 genes. These genes are existing products of nature, naturally occurring within the human body. Myriad located them in nature and merely described their informational content as it exists and functions in nature.

47. Defendant Myriad did not invent, create or in any way construct the differences found when genes are compared or the correlations between certain mutations and an increased risk of breast and/or ovarian cancer. Nature did that. Myriad identified nature's laws.

48. As a result of the breadth of its patents. Myriad has the right to control all genetic testing related to breast and/or ovarian cancer linked to *BRCA*1 or *BRCA*2. Researchers and clinicians cannot develop or implement new tests for

breast/ovarian cancer linked to *BRCA*1 or *BRCA*2 if development or implementation involves looking at *BRCA*1 or *BRCA*2. Women cannot give their blood or DNA to a researcher or clinician and obtain a second opinion. The effect is to infringe on quality medical practice and to compromise quality assurance and improvement of testing.

49. Defendant Myriad has enforced its patent rights over *BRCA*1 and *BRCA*2 genes at least nine (9) times. For example, according to press reports, laboratories at Yale performed analyses of those genes, but they no longer do so as a direct result of a cease-and-desist letter received from defendant Myriad.

50. Defendant Myriad obtained its patents from defendant Patent Office pursuant to a formal written policy by the Patent Office which provides that naturally occurring genes can be patented if they are "isolated from their natural state and purified."

51. An "isolated and purified" human gene performs the exact same function as a non-isolated and purified human gene in a person's body. The information dictated by the gene is identical whether it is inside or outside of the body. According to the Patent Office policy, an "isolated and purified" gene includes one that is simply removed from the body and removed from other content of the cell. Removing a product of nature from its natural location does not make it any less a product of nature.

52. This policy permits the patenting of products of nature, laws of nature, natural phenomena, abstract ideas, and basic human knowledge and

thought. It therefore violates the United States Constitution Article 1, section 8, clause 8 and the First Amendment, as well as 35 U.S.C. § 101 of the patent statute.

53. Defendant Myriad obtained its patents pursuant to the practice of the defendant United States Patent and Trademark Office that permits patenting of comparisons or correlations created by nature, but identified by a patent holder.

54. This practice permits the patenting of laws of nature and abstract ideas and basic human knowledge or thought. It therefore violates Article 1, section 8, clause 8 and the First Amendment of the United States Constitution, as well as 35 U.S.C. § 101.

PATENT CLAIMS OVER NATURAL HUMAN GENES

55. Several of the claims in Myriad's patents cover the human *BRCA*1 and *BRCA*2 genes in their natural, non-mutated form. These include claims 1, 2, 5, and 6 of patent '282 and claim 1 of patent '492.

56. Claim 1 of patent '282 covering *BRCA*1 is for any strand of "isolated" DNA that creates a particular protein identified in the patent. This claim covers the DNA that includes the *BRCA*1 gene in its "wild-type" or non-mutated form. It also includes any DNA that creates any portion of the identified protein. It thus includes DNA sequences that are identical in structure and function to the DNA as it exists in every person's body. It also includes any DNA that creates a fragment of the protein.

57. Claim 2 of patent '282 is very similar, but somewhat narrower. It covers a specific DNA sequence listed in the patent as the DNA sequence for the *BRCA*1 gene.

58. Claim 5 of patent '282 also covers *BRCA*1, but it covers any DNA that has "at least 15 nucleotides" of the DNA referenced in claim 1. A nucleotide is one base. Claim 5 thus explicitly covers small fragments of the *BRCA*1 gene.

59. Claim 6 of patent '282 covers any isolated DNA that has "at least 15 nucleotides" of the DNA referenced in claim 2.

60. Claim 1 of patent '492 is for any strand of "isolated" DNA that creates a particular protein identified in the patent. This claim covers the DNA that includes the *BRCA*2 gene in its "wild-type" or non-mutated form. It also includes any DNA that creates the identified protein. It thus includes DNA sequences that are identical in structure and function to the DNA as it exists in every person's body.

PATENT CLAIMS OVER NATURAL HUMAN GENES WITH NATURAL MUTATIONS

61. Several of the claims in Myriad's patents claim the human *BRCA*1 or *BRCA*2 gene that contains variants or mutations caused by nature. These include claim 1 of '473, claim 7 of '282, and claims 6 and 7 of '492.

62. Myriad looked at human genes from many individuals. Some of those individuals had variants in *BRCA*1 or *BRCA*2. Myriad recorded the DNA sequences of those individuals with those variants

and obtained patents on the DNA with those naturally mutated sequences.

63. Claim 1 of '473 claims "isolated DNA comprising an altered *BRCA*1 DNA having at least one" of the specified variants. Myriad asserts that some of the patented DNA containing specified variants correlate with an increased risk of breast and ovarian cancer. Myriad asserts that other patented DNA containing specified variants does not so correlate or that Myriad does not yet know their effect, if any.

64. Claim 7 of '282 claims "an isolated DNA" that has specified variants. In the text of the patent, Myriad describes all of the variants as cancer predisposing mutations.

65. Claim 6 of '492 claims any "isolated DNA" that creates any mutated form of the protein created by *BRCA*2 if the mutations correlate with a "susceptibility to cancer." In other words, the claim covers any yet-to-be discovered mutations – discovered by anyone -- that correlate with an increased risk of any type of cancer.

66. Claim 7 of '492 also claims isolated DNA if the DNA contains sequences that include any mutations that correlate with an increased risk of cancer.

67. Claim 1 of '473, claim 7 of '282, and Claims 6 and 7 of '492 include DNA sequences that are identical in structure and function to the DNA inside the body of some people.

PATENT CLAIMS OVER ANY METHOD, INCLUDING NON-PATENTED METHODS, OF LOOKING FOR MUTATIONS IN NATURAL HUMAN GENES

68. Myriad's patents also claim any and all methods, including non-patented methods, of looking at natural human genes. This includes Claim 1 of patent '999.

69. Claim 1 of patent '999 covers any method of analyzing a human being's *BRCA*1 gene for the purpose of finding whether the human being has any of the specified germline [inherited] variants.

70. The methods used to look at the gene are not patented and are well known in the field. All that is patented is the act of looking at the *BRCA*1 gene to see if the gene has the specified variants.

PATENT CLAIMS OVER THOUGHT OR ABSTRACT IDEAS

71. Several of the claims in Myriad's patents include comparing two genes, correlations between mutations in the human *BRCA*1 and *BRCA*2 genes that are currently known to be associated with an increased risk of breast and/or ovarian cancer, and correlations between cancer and mutations not now known, but identified in the future. These include claim 1 of '001, claim 1 of '441, claims 1 and 2 of patent '857, and claim 20 of '282.

72. Specifically, claim 1 of '001 involves taking a tumor sample from a person and looking at the *BRCA*1 gene in that sample and comparing it to the *BRCA*1 gene from the same person taken from a part of the body in which there is no tumor and seeing if there are any differences. The methods by which this

is done are not patented. What is patented is performing this comparison of the tumor and germline sequences to identify somatic mutations in the *BRCA*1 gene and thinking "there are differences and they must be somatic (environmentally caused)." What is patented is the abstract idea that nature has made the two forms of the *BRCA*1 genes different.

73. Claim 1 of '441 similarly involves the comparison of two *BRCA*1 genes. This claim covers comparing the *BRCA*1 gene in a tissue sample taken from a person with the *BRCA*1 gene in its "wild-type" or non-mutated state. The methods by which this is done are not patented. What is patented is performing this comparison of the *BRCA*1 gene from the tissue sample and the *BRCA*1 wild-type gene and thinking "there are differences." What is patented is the abstract idea that nature has made the two *BRCA*1 genes different.

74. Patent '857 involves the comparison of two *BRCA*2 genes. Claim 1 involves comparing a *BRCA*2 gene taken from a person with a wild-type *BRCA*2 gene. The methods by which this is done are not patented. What is patented is performing this comparison for *BRCA*2 and thinking "there are differences" and that the differences reflect a mutation. What is patented is the abstract idea that nature has made the two *BRCA*2 genes different.

75. Claim 2 of patent '857 involves the same comparison of two *BRCA*2 genes. The only difference is that the thought that is patented is "there are differences" and they "indicate a predisposition to [breast] cancer." What is patented is the abstract idea that nature has made the two genes different in

a manner that increases that person's risk of breast cancer.

76. Claim 20 of '282 involves "a method for screening potential cancer therapeutics." However, the method consists entirely of putting the potential therapeutic into contact with a cell that includes a *BRCA*1 mutation and looking to see if the cell grows more slowly with the therapeutic than without. That method simply describes a scientific method that has been in place for many years, specifically for a cell with a *BRCA*1 mutation. The only even arguably unique part of the method is the thought that the person has at the end of the process i.e. "this therapeutic worked" when used in the context of a *BRCA*1 mutation or "this therapeutic did not work" in that context.

77. All of these claims (except claim 1 of '857 and claim 20 of '282) include comparisons not only of DNA, but of other derivatives of DNA such as RNA, and cDNA made from mRNA.

78. None of these claims is limited to identifying differences in genes that Myriad has itself identified as correlating with an increased risk of cancer. All identifying of differences, including those that are found in the future by anyone to correlate with an increased risk of cancer, are patented.

79. Myriad did not create any of the differences found in the genes. Nature did. Myriad did not cause any of the effects of those differences. Nature did. All of the effects of these differences occur in a person's body as well as outside the body.

80. None of these claims is limited to "isolated" DNA.

IMPACT OF THE PATENTS

81. Defendant Myriad utilizes its patents by offering a test to determine if an individual has any mutations in the human *BRCA*1 or *BRCA*2 genes. The test consists of sequencing a person's gene, comparing it to either another gene in that person's body or one from another person, and reaching a conclusion about whether nature has caused a variant that increases that person's risk of breast and/or ovarian cancer.

82. There are thousands of doctors and scientists, including molecular pathologists, geneticists, and researchers, around the country, and the plaintiffs, who have the technical ability to look at human genes and who do so on a daily basis. The only thing that prevents those doctors and scientists from looking at the human *BRCA*1 and *BRCA*2 genes is Myriad's patents.

83. One of the conditions for receiving a patent is to disclose publicly all information about the patented thing. The purpose of that requirement is to enable others to "invent around" and build upon and improve the patented thing, thereby fostering scientific progress. Unlike most things that are granted patents, it is not possible to invent around the patented human *BRCA*1 and *BRCA*2 genes or correlations. These genes, their effects, and the correlations between the genes and disease were created by nature and exist in nature. They are pure information, and in order to build upon them, one needs to utilize the patented sequences, which is not permissible under the patents.

84. Because of its patents, Myriad maintains a monopoly over any genetic testing to determine the presence or absence of mutations on the human *BRCA*1 or *BRCA*2 genes. Thus, although others including plaintiffs have the technical ability to determine if a person has a mutation, and are willing to do so using non-patented methods, they can be prohibited from doing so because of the patents on the *BRCA*1 and *BRCA*2 genes and can't tell any patient the results because of Myriad's enforcement of its patents.

85. Because Myriad maintains a monopoly on clinical testing to determine the presence or absence of mutations on the human *BRCA*1 and *BRCA*2 genes, the only types of tests that are offered to patients and the only mutations examined are those dictated by Myriad.

86. Myriad maintains the largest database of *BRCA*1 and *BRCA*2 data. It does not share the information in that database with the Breast Cancer Mutation Database set up by NIH to ensure the widest possible distribution of information about genes and breast cancer.

87. Myriad's monopoly has resulted in a disparity in the amount of information known about genetic mutations in *BRCA*1 and *BRCA*2 in ethnic groups other than Caucasians.

88. Gene patents can serve as a disincentive to innovation in molecular testing because they deny access to a vital baseline of genomic information that cannot be invented around. Moreover, threat of enforcement from a patent holder and ensuing litigation costs lead to a chilling effect as clinical

laboratories are reluctant to develop new tests, even when new tests could directly benefit patients.

89. For at least some portions of the life of the patents, Myriad did not perform certain tests that were known to reveal additional mutations that increased the risk of breast and/or ovarian cancer. Myriad prohibited anyone else from offering those tests to patients even though it knew that they would provide women with essential information about their risk of developing life-threatening cancer. Eventually, Myriad began to offer this additional testing, but chose to package it separately from its standard test.

90. Because of its patents on the *BRCA* genes, Myriad has the power to bar patients from obtaining testing other than through its laboratory. There are women, such as plaintiff Girard and any other women who have obtained full sequencing from Myriad, who cannot obtain a second opinion on their *BRCA* testing and are compelled to make major medical decisions based on a test that they cannot confirm. Plaintiff Limary, who received the result of variant of uncertain significance from Myriad, wants to obtain further testing and for information about her variant to be freely disclosed and studied.

91. Laboratories, such as that operated by Dr. Ledbetter, are increasingly adopting new generations of genetic sequencing technology that will permit faster, more comprehensive and potentially less expensive testing. That testing will be impeded by patents on genes that they cannot test.

92. Myriad charges more than $3,000 for its exclusive Comprehensive BRACAnalysis test. Many

researchers might be able to do the testing for a reduced cost.

93. There are women, including plaintiffs Ceriani and Fortune, who cannot afford the testing offered by Myriad and whose insurance Myriad will not accept. As a result, these women have not been tested.

94. Myriad offers another test, called BRACAnalysis Rearrangement Test or BART, that looks for large genetic rearrangements that are not caught by its standard Comprehensive BRACAnalysis test. Myriad will conduct BART testing for some women who meet its criteria at no additional cost. However, other women must pay an additional price for BART testing – approximately $650.

95. There are women, including plaintiffs Thomason and Raker, who have a significant personal or family history of cancer or who have been advised that they are appropriate candidates for BART testing by their doctors or genetic counselors, but whose BART testing was not included in the price of Myriad's standard Comprehensive BRACAnalysis test. They have not been able to access the BART testing for large rearrangements. The *BRCA* gene patents gave Myriad the power to package this testing separately.

96. Researchers who want to look at the human *BRCA*1 and *BRCA*2 genes for research purposes are prohibited from doing so by the patents without the permission of the patent-holder.

97. Myriad has permitted some researchers to do pure research on the human *BRCA*1 and *BRCA*2 genes. Upon information and belief, Myriad has no

official policy permitting the research and has not publicized its occasional permissiveness. At any time, Myriad can use its patents to prohibit researchers from doing research.

98. Researchers are chilled from engaging in research on the human *BRCA*1 and *BRCA*2 genes by the patents. Researchers are also chilled from engaging in research on other genes. It is increasingly clear that genes interact with other genes in ways that are not yet fully understood. Researchers are chilled from engaging in research on other genes that may interact with the *BRCA*1 and *BRCA*2 genes by the patents.

99. Researchers, such as plaintiffs Dr. Chung and Dr. Ostrer, study women for genetic research. Dr. Chung and some other geneticists believe that if they obtain the results of a particular woman's *BRCA*1/*BRCA*2 test, they are morally obligated to provide that woman with the option to find out the results. Genetic test results used in clinical management should be performed by a CLIA certified clinical diagnostic laboratory, and Myriad is the only such laboratory performing testing for *BRCA*1/*BRCA*2 because Myriad will not permit other clinical laboratories to perform *BRCA*1/*BRCA*2 testing except to a very limited extent.

100. The problems caused by patenting of DNA sequences are not limited to human genes inherited from one's parents. Every human body contains pathogens such as viruses and bacteria that also have DNA and genes. Modern medicine increasingly relies on analysis of the DNA of such entities to develop treatments for disease. If genes are patented, including human genes as well as their

pathogens and commensals, there can be a serious and negative effect on diagnosis and treatment of disease.

101. The effect of the patents has been to stifle clinical practice and research on the genetic predispositions to breast and/or ovarian cancer. The public, and, in particular, women, have suffered unnecessarily as a result.

CAUSES OF ACTION

102. Because human genes are products of nature, laws of nature and/or natural phenomena, and abstract ideas or basic human knowledge or thought, the challenged claims are invalid under Article 1, section 8, clause 8 of the United States Constitution and 35 U.S.C. § 101.

103. All of the challenged claims represent patents on abstract ideas or basic human knowledge and/or thought and as such are unconstitutional under the First and Fourteenth Amendments to the United States Constitution.

PRAYER FOR RELIEF

For all of these reasons, plaintiffs respectfully ask the Court to:

1. Declare invalid and/or unenforceable
    a. Claim 1, 2, and 5, 6, 7 and 20 of patent 5,747,282
    b. Claims 1, 6, and 7 of patent 5,837,492
    c. Claim 1 of patent 5,693,473
    d. Claim 1 of patent 5,709,999

e. Claim 1 of patent 5,710,001

f. Claim 1 of patent 5,753,441

g. Claims 1 and 2 of patent 6,033,857;

2. Enjoin defendants from taking any actions to enforce these claims of these patents;

3. Grant plaintiffs attorneys' fees and costs; and

4. For such other and further relief as the Court deems just and necessary.

Respectfully submitted,

/s/ Christopher A. Hansen

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*Motion for admission to the Southern District of New York bar to be filed

[Declaration of Wendy Chung, filed August 26, 2009] [Caption Omitted] [Exhibit 1 Omitted]

I, Wendy Chung, M.D., PhD, declare under penalty of perjury:

1. I am the Herbert Irving Professor of Pediatrics and Medicine in the Division of Molecular Genetics at Columbia University in New York. I am also Director of Clinical Genetics and Director of Clinical Oncogenetics. I am one of the plaintiffs in this case.

2. I received a B.A. in Biochemistry and Economics from Cornell University in 1990. I received a PhD in genetics from Rockefeller University in 1996 and an MD from Cornell University Medical Center in 1998.

3. I am Board Certified in both Clinical Genetics and Molecular Genetics.

4. I am a member of several professional organizations, including the plaintiff American College of Medical Genetics.

5. I have been conducting research on human genetics for the last 17 years in the areas of obesity, diabetes, breast cancer, pulmonary hypertension, inherited arrhythmias, congenital heart disease and spinal muscular atrophy.

6. I have lectured and published widely on the subject of genetics. I have also received many research grants to do research in the area of genetics. In addition, I am director of the fellowship program in molecular genetics and cytogenetics at Columbia.

7. A full copy of my current curriculum vitae is attached.

8. One of my current areas of research is breast cancer. I have received grants of over $1 million to investigate various genetic aspects of breast cancer.

9. I am the co-investigator of the Breast Cancer Family Registry, funded by the National Cancer Institute of the National Institutes of Health. The goal of the Registry is to collect and study families with multiple cases of breast and/or ovarian cancer and to study genetic and environmental factors influencing cancer susceptibility, clinical outcomes, identify high risk individuals for prevention trials, and study health behaviors. I am responsible for genetic counseling of all patients in the study and serve on the Ashkenazi and Molecular Genetics working groups.

10. In order to study the genetic code of the families in our research, we must sequence their genes. Sequencing of a gene can be done easily by several processes that are all well known and understood by scientists. Sequencing is done in both research and clinical laboratories all over the world. A gene sequence, which is a list of the letters that represent the instructions of the gene, can be examined to determine if it contains any alterations or mutations. Those alterations or mutations can then be further investigated to determine if they have any significance such as for increasing the propensity to a particular disease. Sequencing involves purifying the DNA from the body and from at least some surrounding cellular material and making copies of the gene of interest, but the resultant sequence is functionally identical to the sequence that nature made in the body. The alterations or mutations in the gene that we are able

to identify after sequencing the gene were made by nature, not by the process of sequencing or by me or other scientists, and the effect of those alterations or mutations is dictated by nature, not by any scientist.

11. As part of my molecular genetics research, we sequence human genes, including the BRCA1 and BRCA2 genes of research subjects in my research lab. We look at the sequences to determine if there are any alterations and investigate whether those alterations have clinical significance.

12. We do some of this work in our own lab where we have the personnel, expertise, and facilities necessary to do gene sequencing, including sequencing of the BRCA1 and BRCA2 genes.

13. As a result of the patents owned by Myriad Genetics, I am forbidden from telling the research subjects in my studies the results of their BRCA1 and BRCA2 tests. Even if I determine in my lab that the sample from a particular woman contains a mutation that correlates with an increased risk of breast and/or ovarian cancer, I am prohibited as a result of Myriad's patents from telling that woman any results obtained in my research laboratory alone.

14. As a researcher, I believe I have an ethical responsibility to offer my test subjects access to information about their genes. In order to meet this ethical responsibility, I offer my research subjects the option of finding out their results. As a result of the patents, I can only do that by sending samples to Myriad Genetics to test the sample so I can communicate that information to the patients. That process takes approximately 2-3 weeks.

15. I no longer recall how I learned that Myriad vigorously prohibits labs from sequencing BRCA1 and BRCA2 genes for clinical purposes. That fact is well known and often discussed by molecular geneticists and laboratory directors. I recall hearing about several cease and desist letters from Myriad to other labs, including Yale and University of Pennsylvania. When I became co-investigator of the Registry, it was made clear to me that although we could sequence the BRCA1 and BRCA2 genes for purely research purposes, Myriad would not permit us to do so for clinical purposes.

16. In addition to directing a research laboratory, I also co-direct a clinical molecular genetics laboratory at Columbia. My clinical diagnostic laboratory does not currently do BRCA1 or BRCA2 genetic testing because of the patents. Instead, we send samples to Myriad. I estimate we send approximately 300 samples to Myriad each year.

17. If the patents were invalidated, I would immediately take steps to begin clinical sequencing of the BRCA1 1 and BRCA2 genes. I would offer clinical testing not only to the individuals who participate in the Registry, but also to the broader community of patients at Columbia University, its affiliate hospitals, and hospitals around the country. I would do testing for the named plaintiff women in this case. I would also be in a position to tell the research subjects in my research their genetic test results, and to relay this information promptly.

18. My clinical laboratory has the personnel, expertise, and facilities to do various types of sequencing of the BRCA1 and BRCA2 genes. If the patent were invalidated, we could and would offer

testing that is more comprehensive that that Myriad currently offers. We would offer full sequencing, analysis of deletions, duplications, and rearrangements as one package. This would include genomic analysis that Myriad does not do as part of its standard BRCA1 and BRCA2 sequencing.

19. Myriad relied exclusively on sequencing technology for many years that was unable to detect all mutations in the genes. It was only after considerable pressure from the scientific community that the company added methods to detect these deletions, insertions, and re-arrangements in 2006.

20. Currently, Myriad's test results may report to a patient that she has an alteration but that it is unknown whether the variant increases the risk of breast or ovarian cancer or not. These are often referred to as variants of uncertain significance. As of 2005, approximately 1,433 BRCA1/BRCA2 genetic tests had been reported out by the company to have such variants. These variants are reported disproportionately in minority populations (African Americans, Hispanics, and Asians) because we have less information about the normal genetic variation in minority populations.

21. Our longstanding engagement in and commitment to BRCA1 and BRCA2 research would allow us to do extensive analyses for patients (including but not limited to the named plaintiffs) in the face of a result of "variant of uncertain significance." That would include, for example, looking at whether a variant has appeared in other species, developing a computational model to attempt to predict whether that alteration is disease-causing, analyzing multiple family members for segregation of

the variant with cancer, and analyzing large numbers of unaffected controls from the same ethnic group.

22. I am familiar with the BIC database, which I understand is discussed in detail in Dr. Swisher's declaration. I agree with her that the sharing of data on mutations in the BRCA1 and BRCA2 genes is essential for the advancement of knowledge about the nature of those genes and the clinical significance of the mutations or alterations found. If the patents were invalidated and my clinical lab was permitted to do sequencing, we would share all of the results of our work with the BIC database. I believe such actions would quickly increase knowledge about the alterations in the gene and would result in fewer variants of unknown significance.

23. There is value for patients in having lab tests done in more than one lab. Women who are told they are positive for a mutation of the BRCA1 or BRCA2 genes that correlates with an increased risk of breast and/or ovarian cancer have enormously important decisions to make. It is important that they make those decisions based on accurate information. I have seen instances in which the same genetic test yielded discordant results from two different labs, and it is essential to find out what the correct result is. When only one lab runs a test, it is difficult for that lab to even become aware of possible errors in its testing method. Multiple tests from different labs can ensure that the information patients are using to make those critical and potentially life-altering decisions is accurate.

24. Myriad is willing to perform genetic testing only on blood samples and will not routinely perform

genetic testing on paraffin embedded tissue from previous cancer specimens although this testing is performed in research laboratories such as my own. In many cases, the family member with either breast or ovarian cancer is deceased and the only source of genetic material for testing is a tumor sample that was previously removed. Testing an affected family member is necessary for accurate interpretation of a negative result in other unaffected family members. A negative genetic result in the daughter of a BRCA1 or BRCA2 mutation carrier reduces the daughter's risk of cancer to that of the general population while the cancer risk for a daughter with a negative genetic result of a mother who had early onset breast cancer but was negative for BRCA1 or BRCA2 remains substantially elevated over the general population. If we were able to do testing as a result of the patent's invalidation, we would perform testing on all specimen types.

25. Genes are products of nature and not inventions of man. They are so basic to science that any restriction that prevents scientists from looking at the genes themselves or examining the effects of the genes is fundamentally inconsistent with the advancement of human knowledge.

I declare, pursuant to 28 U.S.C. § 1746. under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Wendy Chung. M.D., PhD

Wendy Chung. M.D., PhD

Executed on July 30, 2009

EXHIBIT 1

[EXHIBIT 1 OMITTED]

[Declaration of Barbara Brenner, filed August 26, 2009] [Caption Omitted In Printing]

1. My name is Barbara A. Brenner. I am Executive Director of Breast Cancer Action ("BCA"). BCA is a Plaintiff in the above-captioned case in its own right and on behalf of its members.

2. Breast Cancer Action is a national not-for-profit organization of approximately 30,000 members. We are dedicated to carrying the voices of people affected by breast cancer in order to inspire and compel the changes necessary to end the breast cancer epidemic. Our members include breast cancer survivors, family members of people diagnosed with breast cancer, and other people affected by or concerned about breast cancer.

3. BCA advocates for policy changes directed at achieving prevention, finding better treatments, and reducing the incidence of breast cancer, provides information about breast cancer to anyone who needs it via newsletters, web sites, e-mail and a toll-free number, and organizes people to get involved in advocacy to advance its policy goals.

4. This case seeks to invalidate patents that have been granted on the BRCA1 and BRCA2 genes. This goal is central to the mission of BCA. Three of our core principles are: people should be able to participate fully in decisions relating to breast cancer treatment; access to information about breast cancer is vital; and people must have access to quality health care. The patents on the BRCA genes make it impossible to advance these principles. BCA cannot encourage researchers and clinicians to perform BRCA1 and BRCA2 related activities, including

genetic testing and research, even when the activities might be aimed at creating new testing methods that Myriad Genetics does not offer or discerning the meaning of uncommon genetic variants. We cannot refer members to or publicize full gene sequencing services at laboratories other than or in addition to Myriad Genetics.

5. The patents limit our work because they are so wide-ranging as to cover the actual BRCA1/2 genetic sequences, mutations, and correlations with cancer, fundamental information that should be shared with all patients, researchers, advocates, and the public. The gene patents have frustrated BCA's advocacy for unfettered research into the causes and treatment of breast cancer. The gene patents also have frustrated BCA's efforts to provide useful information to its members and the public regarding BRCA1/2 genetic testing and information about the significance of BRCA1/2 mutations. For every type of referral we provide, we routinely suggest more than one place to get help or information. This is important for carrying out BCA's educational mission because it is often valuable for someone affected by breast cancer to obtain a second opinion or access more resources. However, for BRCA full sequencing for patients, we can only make one referral — Myriad Genetics, a company whose practices BCA has often criticized.

6. BCA has had to devote its scarce resources into identifying and addressing the problems that result from the BRCA1/2 gene patents and exclusive genetic testing, including staff time for investigating, writing and publishing articles about these problems and advising women who are facing difficult medical situations because the gene patents prevent

alternative testing options or information-sharing. And because the patents extend over the correlation between mutations and hereditary risk of cancer, any publication of that correlation by BCA could be alleged to induce patent infringement, even though one of BCA's main purposes is to educate the public about breast cancer.

7. Many of BCA's members are directly injured by the patents on the BRCA genes. The gene patents create obstacles for patients and their doctors who want information about the BRCA1/2 genes by precluding them from obtaining testing at all or at the laboratory of their choice, from verifying test results at a second lab, or from choosing a laboratory that would share data with researchers. Some of our members have been unable to obtain BRCA genetic testing because of the high cost of the test. Other BCA members face making life-altering decisions without the benefit of a confirmatory test, or have received ambiguous genetic test results that show that they have a genetic variant of uncertain significance. BCA has brought this case on behalf of its members, some of whom are ready, willing, and able to order BRCA1/2 genetic testing and analysis at laboratories other than Myriad Genetics if the patents are invalidated. Elinor Coleman is one such member. She is a BCA member and breast cancer survivor. In 2004, she was tested through Myriad Genetics and was told she has a variant of uncertain significance. She wants additional analysis of her genes to be performed by a laboratory other than Myriad, and is ready, willing, and able to take action to pursue further testing once the patents are no longer in force.

8. To advance its mission, BCA has long expressed concerns about the BRCA1/2 gene patents and Myriad Genetics' exclusive control over genetic testing. For example, I wrote an article for our February/March 1997 newsletter, raising questions about Myriad's commercial goals in gene patenting and genetic testing and the high price of genetic testing (it cost $2400 then, and now costs over $3000). In our May/June 2004 newsletter, we published an article highlighting the differences between testing conducted in the United States and in Europe that have resulted from the more limited enforcement of the patents in Europe. Patents on the BRCA1/2 genes should not determine the availability and quality of genetic testing and the freedom to conduct research.

9. If the patents were invalidated, BCA would immediately use its existing resources to publicize other laboratories for BRCA genetic testing and research opportunities. BCA knows that these alternatives would exist, because it is aware that other plaintiffs in this case, including Dr. Chung and Dr. Oster, would engage in new BRCA-related activities if the patents were not a barrier.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Barbara A. Brenner

Barbara A. Brenner

Executed on August 7, 2009

[Declaration of Vicky Thomason, filed August 26, 2009] [Caption Omitted In Printing]

1. My name is Vicky Thomason. I am a Plaintiff in the above-captioned case.

2. I am a 52-year-old woman living in Kentucky.

3. In 2006, when I was 49 years old, I was diagnosed with cancer in my left ovary.

4. After undergoing surgery and chemotherapy, I consulted with my doctor and a genetic counselor about the best course for further surveillance and treatment. They advised me that I was an appropriate candidate for BRCA genetic testing, based on my personal history and my family history of cancer. My mother was diagnosed with breast cancer at age 48, and my only maternal uncle died at age 69 after being diagnosed with pancreatic cancer. They informed me that if I was positive for a BRCA mutation, I was at higher future risk for breast cancer. My genetic counselor estimated that I had approximately a 23% chance of carrying a BRCA1 or BRCA2 mutation. I decided to be tested in order to help me make informed medical care decisions about screening and other options, which could include prophylactic mastectomy.

5. In September 2007, my doctor ordered Myriad Genetics' Comprehensive BRACAnalysis test for me. I received the following result: "NO MUTATION DETECTED." However, my test results also stated:

> "This test is also designed to detect five specific BRCA1 genomic rearrangements, including a 3.835-kb deletion involving exon 13, a 510-bp

> deletion involving exon 22, a 6-kb insertion involving exon 13, a 7.1-kb deletion involving exons 8 and 9, and a 26-kb deletion involving exons 14-20. The proportion of all BRCA1 genomic rearrangements represented by these specific abnormalities has not yet been characterized. There are other, uncommon genetic abnormalities in BRCA1 and BRCA2 that this test will not detect. This result, however, rules out the majority of abnormalities believed to be responsible for hereditary susceptibility to breast and ovarian cancer..." (emphasis added)

6. My genetic counselor informed me that while my genes were negative for mutations based on Comprehensive BRACAnalysis, 5-10% of mutations are missed by this test. Myriad has an additional test, called BRACAnalysis Rearrangement Testing ("BART"), that she said has a 1-2% chance of finding a missed mutation. BART is offered separately from the first test and requires additional payment. My genetic counselor told me that it was appropriate for me to get BART testing.

7. I was upset when I found out that the test I had received did not look for all known mutations. I had only gotten a partial answer to the question about my hereditary cancer risk. It was important to me to get the additional testing so that I would have more information when making health decisions.

8. I was told that my insurance would not cover the entire cost of BART. My husband and I already have many financial concerns as he is disabled, I

have recently undergone cancer treatment, and our combined income is low. I cannot spend hundreds of dollars on this additional test. I also learned that no other labs offer this test at a lower price, because only Myriad can perform the test.

9. It has been almost two years since I received my negative BRCA mutation test result and since my genetic counselor advised me regarding the supplemental BART test. Because I still cannot afford this test, I continue to face life-altering medical decisions without knowing for sure whether I have a BRCA mutation.

10. If I learned that Myriad's patents on the BRCA1 and BRCA2 genes were invalidated, I would take action right away. I would pursue and order BRCA genetic testing through another laboratory. Without the patents, geneticists and laboratory professionals other than Myriad would be able to offer testing that would look for large rearrangements. I would be able to get more information about my genes and my hereditary breast cancer risk and make life decisions accordingly. This is not just speculation on my part. I understand that some of the other plaintiffs in this case, including Dr. Chung and Dr. Oster, would offer BRCA genetic testing to me if the patents were no longer a barrier. I would immediately seek testing through their laboratories if the patents were no longer in effect.

11. The reason I have not been able to obtain BRCA large rearrangement testing to date is that the gene patents prevent any other laboratory in the United States from performing BRCA testing for patients. As a result, the company that controls the

patents can decide what tests to offer, how to offer them, and how much to charge for each. If the patents were invalidated, I could finally obtain the large rearrangement analysis of my genes that was not performed when I was first tested and could more fully understand my genes and my hereditary risk for cancer.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/Vicky Thomason

Vicky Thomason

Executed on August 8, 2009

[Declaration of Kathleen Raker, filed August 26, 2009] [Caption Omitted In Printing]

1. My name is Kathleen Raker. I am a Plaintiff in the above-captioned case.

2. I am a 42-year-old woman living in Pennsylvania.

3. Since I was a child, I have been concerned about my risk for breast cancer. My mother was diagnosed with advanced breast cancer at age 26 and died less than two years later, when I was three years old. About ten years prior to my mother's death, her mother — my grandmother — also died of breast cancer.

4. I have never been diagnosed with cancer. In November 2004, I had a biopsy because my doctor was concerned about a suspicious rash on my breast that had been there for several months. The biopsy fortunately turned out negative.

5. Afterwards, I enrolled in a special breast surveillance clinic. Upon learning about my family history, my doctor at that clinic recommended that I obtain genetic counseling. I met with a genetic counselor. After reviewing my family history in detail, my genetic counselor presented the option of testing for BRCA1 and BRCA2 genetic mutations, which indicate a higher future risk of breast and ovarian cancers. My genetic counselor facilitated genetic testing with my doctors. I knew that the test results could be crucial information to help me make the most informed medical decisions, including decisions about screening and prevention options.

6. In April 2007, my doctor ordered Myriad Genetics' Comprehensive BRACAnalysis test for me. I received the following result: "NO MUTATION DETECTED." However, my test results also stated:

> "This test is also designed to detect five specific BRCA1 genomic rearrangements, including a 3.835-kb deletion involving exon 13, a 510-bp deletion involving exon 22, a 6-kb insertion involving exon 13, a 7.1-kb deletion involving exons 8 and 9, and a 26-kb deletion involving exons 14-20. The proportion of all BRCA1 genomic rearrangements represented by these specific abnormalities has not yet been characterized. There are other, uncommon genetic abnormalities in BRCA1 and BRCA2 that this test will not detect. This result, however, rules out the majority of abnormalities believed to be responsible for hereditary susceptibility to breast and ovarian cancer..." (emphasis added)

7. I was informed that my BRCA test results were negative, finding no deleterious mutation on my BRCA1 or BRCA2 genes. However, my counselor explained to me that I could still be at hereditary risk due to a mutation in my BRCA genes that could not be detected in the initial test. She told me about a second test that can identify additional mutations that are not detected in Myriad's "Comprehensive BRACAnalysis." This second test, also offered by Myriad Genetics, is entirely separate from the first test and would cost an additional $650

to perform. She presented this second test as a follow-up option for me.

8. I was frustrated to learn that the test I had received did not look for all the mutations on my BRCA1 and BRCA2 genes that are known to the scientific community. I couldn't feel sure about my results -- I was not really negative for all BRCA mutations, just the ones that they looked for in that first test. I learned that the second test looks for large rearrangements in my BRCA genes that cannot be detected by the first test. Given my family history, it is very important to me to know whether BRCA genetic mutations are something I need to factor into my medical care. Long-term, it is also important for my two children and their future children to have this information about my genes so that they can consider testing, screening and prevention at the appropriate time. Without this information, my family may be lulled into a false sense of security only to once again be taken by surprise by a family member's cancer diagnosis at an early age and incurable stage. I wanted to order this additional test.

9. However, I could not then, and still cannot, afford to pay $650 out-of-pocket for the second test. My family has struggled financially in recent years. Our economic situation has jeopardized our health insurance. My two sons are covered through the government's Children's Health Insurance Program ("CHIP"). My husband and I have insurance but have often fallen behind in making payments, and as a result, our coverage is unstable and insecure.

10. I also learned that there is no lab other than Myriad where I could get large rearrangement or confirmatory testing done, because Myriad controls patents over the BRCA genes. That means that I cannot order large rearrangement testing from another lab at a lower price, or as part of a complete test. I also cannot get verification of the negative result that I received. It is my understanding that even for research purposes, other labs could not tell me whether they see new mutations in my BRCA genes using new testing methods.

11. To date, I still have not obtained Myriad's BRACAnalysis Rearrangement Testing ("BART"), or any other large rearrangement testing, to determine if I have a BRCA mutation that would have been missed by the first "comprehensive" test. I face stressful questions about how to best protect my health without this significant piece of information about my genes. I am particularly worried about the difference this information would make for me with respect to ovarian cancer, because doctors often cannot identify ovarian cancer at an early stage. If I were positive for a BRCA mutation, I would probably have an oophorectomy in order to reduce the likelihood that I will ever experience breast or ovarian cancer. If I learned that I am in fact positive for a BRCA mutation, I would also be more apt to consider chemo-prevention and further steps to ensure adequate screening for breast cancer.

12. If I learned that Myriad's patents on the BRCA1 and BRCA2 genes were invalidated, I would take action right away. I would pursue and order BRCA genetic testing through another laboratory. Without the patents, geneticists and laboratory

professionals other than Myriad would be able to offer testing that would look for large rearrangements. I would be able to get more information about my genes and my hereditary breast cancer risk and make life decisions accordingly. This is not just speculation on my part. I understand that some of the other plaintiffs in this case, including Dr. Chung and Dr. Ostrer, would offer BRCA genetic testing to me if the patents were no longer a barrier. I would immediately seek testing through their laboratories if the patents were no longer in effect.

13. The reason I have not yet gotten BRCA large rearrangement testing is that the gene patents prevent any other laboratory in the United States from performing BRCA testing for patients. As a result, the company that controls the patents can decide what tests to offer, how to offer them, and how much to charge for each. If the patents were invalidated, I could finally obtain the large rearrangement analysis of my genes that was not performed when I was first tested and could more fully understand my genes and my hereditary risk for cancer.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Kathleen Raker

Kathleen Raker

Executed on August 8, 2009

[Declaration of Genae Girard, filed August 26, 2009] [Caption Omitted In Printing]

1. My name is Genae Girard. I am a Plaintiff in the above-captioned case.

2. I am a 39-year-old woman living in Texas.

3. In July 2006, when I was 36 years old, I was diagnosed with breast cancer in my left breast. After consulting with a genetic counselor and other doctors about the best course of treatment, I decided to have genetic testing performed to help assess my hereditary risk of cancer and how aggressive my treatment should be. Because a BRCA mutation would indicate that I was at a high future risk of another occurrence of breast cancer and of ovarian cancer, I knew that the test results could be crucial in making my medical decisions.

4. I was tested in December 2006 and was informed that I was positive for a deleterious mutation on my BRCA2 gene. My doctors told me that the positive result should be a major factor in deciding whether to get prophylactic bilateral breast surgery and ovarian surgery, particularly because it is difficult to screen for ovarian cancer.

5. I asked if I could get the test results verified through another lab. I know that no medical test can be perfectly accurate in every situation and that laboratories and doctors sometimes make mistakes. I also know that laboratories perform different types of tests, and that it can be useful to have your samples tested using more than one method. Once I was diagnosed, I

promised myself to get second or third opinions on test results and proposed courses of treatment.

6. However, I was told that, for this important test which raised the question of prophylactic, surgical removal of both my breasts and ovaries, I could not have another laboratory perform the testing. No laboratory other than Myriad Genetics could perform full sequencing of the BRCA genes. I learned that Myriad was the only lab that could do this testing because it controlled patent rights over the BRCA1 and BRCA2 genes.

7. I faced life-altering decisions without being able to verify my test results. Bilateral breast and ovarian surgeries reduce one's risk of cancer, but they are also major procedures that require long periods of recovery and the premature and permanent loss of hormones, with possibly serious side effects. Oophorectomy also ends the future possibility of having children.

8. My genes also have implications for my family members. Because I tested positive for a particular mutation, genetic testing guidelines provide that my family members who want to pursue testing should receive a type of test that looks specifically for the mutation that has been identified on my BRCA2 gene. I would not want my family's testing to be based on my single result either.

9. Two and a half years have now passed, and I still live with the uncertainty and frustration that comes from not being able to confirm my BRCA2 positive test result.

10. If I learned that Myriad's patents on the BRCA1 and BRCA2 genes were invalidated, I would

take action right away. I would pursue and order BRCA genetic testing through another laboratory. Without the patents, geneticists and laboratory professionals other than Myriad would be able to offer BRCA full sequencing. I would be able to confirm that my BRCA2 gene does have the identified mutation and make life decisions accordingly. This is not just speculation on my part. I understand that some of the other plaintiffs in this case, including Dr. Chung and Dr. Ostrer, would offer BRCA genetic testing to me if the patents were no longer a barrier. I would immediately seek testing through their laboratories if the patents were no longer in effect.

11. The reason I have not been able to obtain a second BRCA genetic test to date is that the gene patents prevent any other laboratory in the United States from performing BRCA full sequencing for patients. If the patents were invalidated, I could finally get another test done and more fully understand my genes and my hereditary risk for cancer.

I declare, pursuant to 28 U.S.C, § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/Genae Girard

Genae Girard

Executed on August 9. 2009

[Declaration of Runi Limary, filed August 26, 2009] [Caption Omitted In Printing]

1. My name is Runi Limary. I am a Plaintiff in the above-captioned case.

2. I am a 32-year-old Asian-American woman living in Texas.

3. When I was 28 years old, I found a lump in my right breast. I was told by my doctor that I was too young to have cancer. It was only after I insisted that my doctors look further that I was diagnosed with an aggressive breast cancer, in November 2005.

4. After my diagnosis, my doctor advised me that I was an appropriate candidate for BRCA genetic testing, especially because of my age. People with BRCA mutations are more likely to experience cancer at younger ages. I decided that I wanted to get the testing, because if I had a BRCA mutation, I would be at higher future risk of breast and ovarian cancers and could make treatment decisions accordingly. But my insurance plan did not cover the test, and I could not afford to pay the $3000 cost of the test out-of-pocket. I was forced to make important medical decisions without knowing whether I was positive for a mutation.

5. I was not able to get tested until nearly two years after my diagnosis. I switched jobs, and my new insurance policy covered the Comprehensive BRACAnalysis test offered by Myriad Genetics. In November 2007, I received my test results: "GENETIC VARIANT OF UNCERTAIN SIGNIFICANCE." The results showed "No Mutation Detected" for my BRCA2 sequence and a genetic

variant of "Uncertain Significance" for my BRCA 1 gene.

6. I was surprised and disturbed by these results. I had not known that this was a possible outcome -- that I could have a mutation but not know whether it was connected to a higher risk of cancer. I called Myriad Genetics and was told that this variant had been identified in other women of Asian descent but that they did not know whether it was correlated to cancer.

7. Later, I discovered that I could not get BRCA sequencing done at a lab other than Myriad's, and that there was additional testing offered through Myriad that I had not received that looked for certain large rearrangements along the BRCA genes. This additional test, called BART, is a separate test that costs approximately $650. I also learned that variants of uncertain significance are disproportionately found in women who belong to minority racial groups.

8. I want to make the most informed health and medical decisions for myself, but it is difficult to weigh my options when I do not know the significance of the genetic variant I have. I am deeply concerned that the patents are a barrier for minority women who want to be tested and for scientists who want to uncover the significance of variants such as the one in my genes. A commercial laboratory may not have much financial incentive to determine the meaning of a mutation that tends to appear in a small percentage of the population in the U.S., like women of Asian descent. If I knew I was positive for a deleterious mutation, I would choose to have an oophorectomy (ovarian surgery), because screening

methods for ovarian cancer often do not detect cancer until it has advanced. But I do not have any children and do not want to end my ability to have children by removing my ovaries unless my risk of cancer is high.

9. If I learned that Myriad's patents on the BRCA1 and BRCA2 genes were invalidated, I would take action right away. I would pursue and order additional BRCA genetic testing through another laboratory. Without the patents, geneticists and laboratory professionals other than Myriad would be able to offer BRCA full sequencing. I would be able to verify my results and have my genes tested using other methods, and make life decisions accordingly. This is not just speculation on my part. I understand that some of the other plaintiffs in this case, including Dr. Chung and Dr. Ostrer, would offer BRCA genetic testing to me if the patents were no longer a barrier. I would immediately seek testing through their laboratories if the patents were no longer in effect. Dr. Chung also has stated that she would conduct further testing and analysis to determine the meaning of variants of uncertain significance, including the variant I have, and I would immediately agree to participate in this testing and analysis. I would choose to participate with a laboratory that will share its data, including the data about my variant, with other researchers.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Runi Limary

Runi Limary

Executed on August 10, 2009

[Declaration of Harry Ostrer, filed August 26, 2009] [Caption Omitted In Printing] [Exhibit 1 Omitted]

1. My name is Harry Ostrer, M.D.. I am Professor of Pediatrics, Pathology, and Medicine at New York University School of Medicine and also the Director of the Human Genetics Program in the Department of Pediatrics and Director of the Molecular Genetics Laboratory of NYU Langone Medical Center. In 2007, I was appointed Associate Director of Genetic Epidemiology for the NYU Clinical Translational Science Institute. I am one of the plaintiffs in this case.

2. I received my B.S. from the Massachusetts Institute of Technology in 1972 and my M.D. from Columbia University in 1976. I completed a post doctoral internship and residency at Johns Hopkins Hospital in 1976 and 1978, respectively. I was a Clinical Associate in the Neonatal and Pediatrics Medicine Branch & Laboratory of Molecular Genetics for the National Institute of Child Health and Human Development of the National Institutes of Health from 1978 to 1981. I was then a Postdoctoral Fellow in Genetics in the Department of Pediatrics at Johns Hopkins University School of Medicine from 1981 to 1983. After serving on the Medical faculty at the University of Florida, I was appointed to the faculty of Pediatrics, Pathology, and Medicine at New York University School of Medicine in 1990, and Director of the Human Genetics Program in the Department of Pediatrics. In that capacity, I established the Molecular Genetics Laboratory of NYU Langone Medical Center.

3. I am Board Certified in Clinical Genetics, Pediatrics, Clinical Cytogenetics and Clinical Molecular Genetics. I am a member of the plaintiff American College of Medical Genetics. I have lectured and published widely on the subject of genetics. Articles I have authored or co-authored have appeared in *Nature, New England Journal of Medicine, American Journal of Human Genetics, American Journal of Medical Genetics,* and *Genomics,* and I have served on the Editorial Board of *Clinical Genetics.* I have also received many research grants to do research in the area of genetics. A copy of my curriculum vitae is attached hereto as Exhibit 1.

4. Through the Human Genetics Program and Molecular Genetics Laboratory at the NYU Langone Medical Center that I direct, my staff and I engage in both research and clinical practice relating to genetic related susceptibility to disease. Comprehensive information about the work we perform through the lab is available from our website at http://pediatrics.med.nyu.edu/genetics. While I have the capability and desire to do so, I cannot provide patients with the results of BRCA1/2 related genetic screening for their susceptibility to breast cancer because I am forbidden to do so as a result of Myriad's assertion of its patents. The details of that assertion by Myriad are as follows.

5. In the late 1990's, my lab was sending patient samples to Dr. Haig Kazazian at the University of Pennsylvania for BRCA related genetic screening. Then, in or around 1998 or 1999, I was informed that Dr. Kazazian would no longer accept samples and provide such service to me or anyone else because his

lab was ceasing all such operations as a result of patent infringement assertions made against them by Myriad. As a result, since Myriad became and still is the only other provider of BRCA1/2-related genetic screening services, my program began sending all patient samples to them for analysis. Currently, we send Myriad approximately 500-800 patient samples for BRCA related genetic screening every year, the vast majority of which are from patients living in New York.

6. I am also aware that Myriad has vigorously defended its patent rights related to the BRCA1/2 genes in Europe and this aggressive patent behavior has contributed to the chilling effect Myriad's patent assertion has had on other labs considering offering BRCA1/2 related genetic testing services. In my opinion, Myriad's assertion of its patents has frightened off others from even applying for the required CLIA approval necessary to offer BRCA1/2 related genetic testing in the United States. I know that, personally, as a result of what Myriad did to Dr. Kazazian's lab, I have never even tried to apply for such approval for my lab, because I am certain that Myriad would make the same patent infringement allegations against me if I did so.

7. Supporting my belief on this subject is the fact that Myriad, in May of 1998, demanded I enter into a license agreement if I wanted to offer even a very limited amount of BRCA1/2-related genetic testing. On May 21, 1998, I received a letter from Mr. William A. Hockett, Director of Corporate Communications for Myriad, that stated, "I understand that you are either currently providing diagnostic testing services for BRCA1 or are

interested in initiating such a service," before notifying me that, "Myriad Genetics has been awarded four US patents covering BRCA1." A copy of the letter is attached hereto as Exhibit 2. The patents referenced in the letter were listed in an attached proposed license agreement (there were actually five, not four, patents specifically identified in the license agreement) and they are the exact same patents that are involved in this case relating to BRCA1. Mr. Hockett's letter indicated that Myriad was offering me a very limited license only to do single mutation tests and multiple mutation panels (up to four mutations) for patients of Ashkenazi Jewish descent. The narrow license Myriad offered to me would not allow my lab to do full BRCA1/2-related genetic testing and, so, I did not enter into one with them. Whereas it is true that some years have passed since that letter, I have no reason to believe that Myriad's position that my offering such testing would violate their patents has changed, as I understand the cited patents are still in effect.

8. If the patents were invalidated, I would immediately take steps to begin clinical sequencing of the BRCA1 and BRCA2 genes. I would receive samples not only from patients at NYU's hospitals but from other hospitals and referring physicians around the country. I would also specifically do sequencing for the named plaintiff women in this case and I would offer such testing on a sliding cost scale based upon the patient's income and wealth and that would include zero cost for patients who cannot afford to pay for the test and who do not have insurance to cover the test. Approximately 10% of the genetic testing we currently perform for patients is

provided to them by us for free and I expect the same to be true of our BRCA1/2-related testing if we are enabled to begin offering it.

9. My laboratory has all of the personnel, expertise, and facilities necessary to do various types of sequencing of the BRCA1 and BRCA2 genes and I have the strong desire for my lab to provide such sequencing services. We could, and would, as necessary, do full sequencing, search for deletions and rearrangements, and search for large rearrangements. This would include sequencing that Myriad does not do as part of its standard BRCA1 and BRCA2 sequencing.

10. Further, if the patents were invalidated, I would begin to tell patients involved in my current research program regarding susceptibility to breast cancer the results of their BRCA1/2-related genetic screening. As of now, I understand Myriad would consider such action on my part to be infringement of their patents. However, it is important, for research purposes, to study the way patients respond after being told their genetic testing results, as this can lead to valuable insights regarding their behavior. I do not provide the results of BRCA 1/2-related genetic screening to the patients in my research today because I assume that such disclosure is not allowed as a result of Myriad's other patent assertion activities. Such research would also be beneficial for prospective analysis and could aid medical science in improving patient care.

11. Because of their patent assertion, Myriad is the only lab in the nation from which my patients can get BRCA1/2-related genetic screening. I think it is important for there to be more than one lab that

offers a particular genetic test, because the methodology or results provided by one lab may not correspond with that of another. This doesn't mean one lab is necessarily wrong or bad, but just that reasonable minds can disagree about the best way to perform such tests and analyze such results. Thus, it is important that patients have access to more than one lab for performing BRCA 1/2-related genetic tests. Women who are told they are positive for a mutation of the BRCA1 or BRCA2 genes that correlates with an increased risk of breast and/or ovarian cancer have enormously important decisions to make. Likewise, women who are told from Myriad's test that they are negative for a mutation of the BRCA1 and BRCA2 genes may still harbor a mutation that places them at significant risk. It is important that they make those decisions based on accurate information. Tests from different labs can ensure that the information they are using to make those decisions is accurate with regard to test performance and interpretation. This is one reason why, if the patents are invalidated, my lab will immediately begin to offer such testing.

12. Another harm caused by having only a single lab performing genetic testing, such as with Myriad and the BRCA genes, is that research into variants of unknown significance cannot be performed. Many of my patients who send samples to Myriad get results that indicate they have an alteration, but that it has unknown significance. This means Myriad doesn't know whether the alteration is a mutation relating to an increased susceptibility to breast and ovarian cancer, or is instead an insignificant alteration of no consequence. By not being able to do independent BRCA1/2 genetic testing and analysis, the ability to

determine the meaning of these unknown variants is stymied and at the whim of Myriad's corporate interests. It may very well not be in the financial interests of Myriad to do further research on variants of unknown significance from smaller or underrepresented population groups, like racial minorities, and thus such research would not happen at all unless another lab — and in particular an academic lab like mine — has the opportunity to do so. This is yet another reason why my lab would immediately begin to perform BRCA1/2-related genetic testing upon invalidation of the Myriad patents, to aid BRCA1/2-related research on many fronts, including into the meaning of what are currently variants of "unknown significance."

13. I am aware of the BIC database, which I understand is discussed in detail in Dr. Swisher's declaration. I agree with her that the sharing of data on mutations in BRCA1 and BRCA2 genes is essential for the advancement of knowledge about the nature of those genes and the clinical significance of the mutations or alterations found. Currently, we must sometimes report that we have found an alteration but don't know whether it increases the risk of breast or ovarian cancer or not. These are often referred to as variants of unknown significance. If the patents were invalidated and my lab was permitted to do sequencing, we would share all of the results of our work with the BIC database. Such actions would quickly increase knowledge about the alterations in the gene and would result in fewer and fewer alterations whose significance is unknown.

14. Genes are products of nature and not inventions of man. They are so basic to science that

any restriction that prevents scientists from looking at the genes themselves or examining the effects of the genes is fundamentally inconsistent with the advancement of human knowledge.

I declare, pursuant to 28 U.S.C. §1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Harry Ostrer, M.D.

Harry Ostrer, M.D.

Executed on August 11, 2009

EXHIBIT 1

[EXHIBIT 1 OMITTED]

EXHIBIT 2

Myriad

May 21,1998

Harry Ostrer, M.D.
NYU Medical Center
550 First Avenue
Room MSB136
New York, NY 10016

Dear Dr. Ostrer:

I understand that you are either currently providing diagnostic testing services for BRCA1 or are interested in initiating such a service. Accordingly, I have enclosed Myriad's Standard Collaboration Agreement relating to BRCA1 testing.

Myriad Genetics has been awarded four US patents covering BRCA1. These patents cover (i) 47 individual mutations including the BRCA1 mutations common in the Ashkenazi Jewish population (185delAG, 5382insC); (ii) predisposition diagnostic testing for these deleterious mutations; (iii) diagnostic testing of tumor samples for alterations in BRCA1; (iv) composition of matter covering the BRCA1 gene, any fragments of the BRCA1 gene and primers of the BRCA1 gene; and (v) use of the BRCA1 gene in diagnostic testing for breast and ovarian cancer susceptibility.

For a limited period of time, Myriad Genetics is going to offer collaboration licenses to select Universities, laboratories and cancer centers to perform BRCA1 testing using the Company's patented mutations and technology. The Company is pleased to offer such a collaboration license to NYU Medical Center. The Agreement covers single mutation tests and multiple mutation panels (up to four mutations) to allow for testing patients of Ashkenazi Jewish descent. The Agreement specifies a modest fee per test without any up-front license fee or minimum annual royalty.

If you have any questions or comments concerning this agreement, please call me at the number listed below. I look forward to your reply.

Yours sincerely,

/s/ William A. Hockett

William A. Hockett
Director of Corporate Communications
Phone: (801) 584-3504
Fax: (801) 584-3518
email: bhockett@myriad.com

Myriad Genetics, Inc.
320 Wakara Way
Salt Lake City, UTAH 84108
(801) 584-3600
FAX (801) 584-3640

COLLABORATION AGREEMENT

This Non-Exclusive Collaboration Agreement (hereinafter "Agreement"), effective the ______day of ______, 1998 is between Myriad Genetics, Inc. (hereinafter referred to as "Myriad"), having a business address at 320 Wakara Way, Salt Lake City, Utah 84108, and NYU Medical Center (herein after referred to as "NYU"), located at 550 First Avenue, Room MSB136, New York, New York 10016.

WHEREAS, Myriad holds rights to certain Patents relating to the human BRCA1 gene, which Patents are described in Appendix A, attached hereto; and

WHEREAS, NYU desires to receive a non-exclusive license to utilize said Patents, in order to develop, and seek and obtain regulatory approval for, certain testing services to be performed by NYU; and

WHEREAS, Myriad and NYU desire to collaborate on certain ongoing research activities concerning the human BRCA1 gene and predisposition to breast or ovarian cancer.

NOW, THEREFORE, the parties hereto, intending to be legally bound hereby, agree as follows:

1. Definitions.

1.1. An "Affiliate" is any person, corporation, firm, partnership or entity, whether *de jure* or *de facto,* which directly or indirectly owns, is owned by, or is under the common ownership of a party to this Agreement to the extent of at least fifty percent (50%) of the equity of the owned entity, having the power to vote on or direct the affairs of the owned entity, and any person, corporation, firm, partnership, or other entity actually controlled by, controlling or under common control with a party to this Agreement.

1.2. "Patents" means those patents or patent applications listed on Appendix A; and any patents or patent applications which claim the BRCA gene or uses of the BRCA1 gene, which are owned by Myriad or are subject to assignment or license, in whole or in part, to Myriad. Included within the definition of Patents are any continuations, continuations-in-part, divisions, patents of addition, reissues, renewals or extensions thereof.

1.3. "Research Tests" shall mean tests under an IRB approved protocol for the presence or absence of BRCA1 mutations for the purposes of furthering non-commercial research programs, the results of which are not provided to the patient and for which no money is received from the patient or the patient's insurance.

1.4. "Testing Service" shall mean medical laboratory testing under an IRS approved protocol for the presence or absence of BRCA1 mutations for the purpose of determining or predicting predisposition to, or assessing the risk of breast or ovarian cancer in humans. For the purposes of this Agreement, Testing Services shall include only mutation-specific screening tests which are performed to detect a maximum of four mutations per test.

2. Grant of Rights and Collaborative Activities.

2.1. Myriad hereby grants NYU the non-exclusive right under the Patents to develop and use Research Tests and to develop, market, use and sell Testing Services in the United States of America; provided, however, that Research Tests and Testing Services shall only be performed pursuant to protocols and procedures reasonably acceptable to Myriad and approved by Myriad in writing prior to the performance of any such Research Tests and Testing Services. NYU may extend such rights to any Affiliate which is an educational or non-profit corporation upon written notice to Myriad and upon written agreement of such Affiliate to be bound by all terms and provisions hereof (a "Permitted Affiliate"). NYU shall have no right to grant sublicenses or to conduct any such Testing Services or Research Tests through any non-Affiliates without Myriad's consent.

2.2. The rights conveyed herein by Myriad are in all respects subject to the terms and conditions of this Agreement, including without limitation the warranties of NYU contained in Section 5 hereof.

2.3. Myriad and NYU agree to collaborate in the following activities:

a) NYU shall conduct such academic research activities as it shall determine involving BRCA1 and shall keep Myriad generally advised of the work of its research faculty in conducting such research. NYU may publish the results of such research, provided that no confidential or proprietary information of Myriad is disclosed. Myriad shall be provided with a copy of the manuscript of any such publication at least thirty (30) days prior to submission for publication.

b) Myriad may, from time to time and in its sole discretion allow NYU faculty members to send samples to Myriad's laboratory facilities for testing at reduced rates in order to support research activities involving BRCA1 or other disease predisposing genes.

2.4. NYU hereby grants Myriad (i) a right of first refusal to obtain an exclusive license to commercialize any invention resulting from activities of NYU pursuant to this Agreement under terms to be negotiated in good faith and (ii) a non-exclusive, royalty-free license under any invention resulting from activities of NYU pursuant to this Agreement relating to testing for the presence or absence of BRCA1 mutations.

2.5. NYU shall have the right to perform Research Tests provided that no fee is charged for such tests and provided that no direct clinical use shall be made of any Research Test results.

2.6. NYU shall have the right to perform Testing Services at NYU but only to the extent that such Testing Services are ordered by physicians affiliated with NYU or its Affiliates. As consideration for such rights NYU shall pay to Myriad an amount equal to (i) $30 for tests to detect a single mutation, and (ii) $45 per test for all other Testing Services actually performed. Additionally, NYU shall agree that, in exchange for the licenses granted hereunder, NYU and its Permitted Affiliates shall use Myriad to perform all other BRCA1 tests covered by patents owned or controlled by Myriad which are ordered by physicians through NYU or its Permitted Affiliates during the term of this Agreement.

2.7. NYU shall keep and require its Permitted Affiliates to keep complete and accurate records of all Testing Services and Research Tests performed. Myriad shall have the right at its expense to audit the performance of Research Tests and Testing Services and laboratory protocols, testing procedures, and quality control procedures at NYU, provided that confidentiality of patient records shall at all times be maintained by NYU. Myriad shall also have the right at its expense, through a certified public accountant or like person reasonably acceptable to NYU, to examine such records relating to Testing Services during regular business hours during the life of this Agreement and for six (6) months after its termination; provided, however, that such examination shall not take place more often than once a year, and shall not cover such records for more than the preceding three (3) years and provided further that such accountant shall report to Myriad only as to the accuracy of such sales and the payments required pursuant to this Agreement.

2.8. Within thirty (30) days after the close of each calendar quarter, NYU shall deliver to Myriad a true accounting of all Testing Services performed by NYU and its Permitted Affiliates during such quarter, and shall at the same time make all payments due to Myriad pursuant to this Agreement.

2.9. Late payments shall be subject to an interest charge of one and one-half percent (1 1/2%) per month.

3. Term of Agreement.

3.1. This Agreement shall commence upon the date first written above and continue for a period of three years unless sooner terminated by mutual consent of the parties, which consent shall not be unreasonably withheld. This Agreement may be renewed for additional periods of three years upon mutual agreement of the parties.

3.2. Notwithstanding the foregoing, the obligation to make payments pursuant to Section 2.6 of this Agreement shall expire upon the expiration, lapse or invalidation by a decision of a court or tribunal of competent jurisdiction from which no appeal is or can be taken, of the last remaining Patent in the United States of America which contains a valid and unexpired claim covering IIRCA1, or its use, in the United States of America.

4. Confidentiality.

4.1. Myriad and NYU may each, in the course of collaborative activities under this Agreement, receive confidential and proprietary information from the other party. Each party agrees to maintain such information (which shall be marked or otherwise identified by the disclosing party as confidential) in confidence and will not use such information for any purpose except as authorized hereunder. Each party shall exercise, and shall cause its Affiliates, to exercise, a reasonable degree of care and at least the same degree of care as it uses to protect its own confidential information of similar nature to preserve the confidentiality of confidential information disclosed by the other party. Each party shall safeguard such information against disclosure to third parties, including without limitation employees and persons working or consulting for such party that do not have an established, current need to know such information for purposes authorized under this Agreement. This obligation of confidentiality does not apply to information and material that:

4.1.1. were properly in the possession of the receiving party, as shown by written records, without any restriction on use or disclosure, prior to receipt from the other party;

4.1.2. are at the time of disclosure hereunder in the public domain by public use, publication, or general knowledge;

4.1.3. become general or public knowledge through no fault of the receiving party or its Affiliates following disclosure hereunder;

4.1.4. are properly obtained by the receiving party from a third party not under a confidentiality obligation to the disclosing party hereto; or,

4.1.5. are required to be disclosed by order of any court or governmental authority; however, the receiving party shall provide the disclosing party with immediate notice of such required disclosure so that the disclosing party may have the opportunity to contest such disclosure.

4.2. Neither party shall make a public announcement or other publication regarding this

Agreement (whether as to the existence or terms hereof) without the prior, written consent of the other, which consent shall not be unreasonably withheld; provided that the foregoing shall not prohibit any disclosure which, in the opinion of counsel to the disclosing party, is required by any applicable law or by any competent governmental authority.

5. Liability and Warranties

5.1. Myriad warrants that it has all power and authority to enter into this Agreement and to consummate the transactions contemplated hereby.

5.2. EXCEPT AS SET FORTH IN THIS PARAGRAPH 5, MYRIAD DISCLAIMS ANY AND ALL REPRESENTATIONS AND WARRANTIES, WHETHER EXPRESS OR IMPLIED, PERTAINING TO THE RESEARCH TESTS OR TESTING SERVICES OR THE PATENTS LISTED IN EXHIBIT A, INCLUDING BUT NOT LIMITED TO ANY IMPLIED WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE OR NON-INFRINGEMENT.

5.3. NYU warrants that it is an educational or non-profit corporation, duly organized under the laws of and has full power and authority to enter into this Agreement and to consummate the transactions contemplated hereby.

5.4. NYU warrants that it has all necessary regulatory approvals at the state and federal level to perform Research Tests and Testing Services. NYU further warrants that it will at all times conform to the protocols and procedures as reviewed and approved by Myriad pursuant to Section 2.1 hereof.

6. Infringement

6.1. NYU shall promptly inform Myriad of any suspected infringement, infringement or misappropriation, by any third party, of Patents.

6.2. Myriad may bring suit with respect to Patents on its own and shall bear all costs of, and shall exercise all control over, any such suit. Myriad may, at its expense, cause Licensee to be joined in the suit as a plaintiff. Recoveries, if any, whether by judgment, award, decree or settlement, shall belong solely to Myriad. Any expenses incurred by NYU as a result of being added to such suit by Myriad shall be reimbursed by Myriad.

7. Indemnification.

7.1. Myriad shall not under any circumstances be liable to NYU or any third party for claims for any incidental, consequential, indirect or special damages, including any lost profits or savings, arising from any breach of warranty or the performance or breach of any other provision of this Agreement or the use or inability to use the Patents, or for any claims arising in tort, personal injury, product liability, or patent infringement.

7.2. NYU agrees to, at its expense, defend, indemnify and hold Myriad and its Affiliates harmless from and against any costs, expenses, or damages resulting from, or otherwise arising out of Research Tests or Testing Services performed by NYU, including, without limitation, the advertising or selling of Testing Services by NYU.

7.3. Indemnification provided Myriad under this Agreement shall extend also to Myriad's Affiliates, officers, directors, shareholders, successors, assigns, agents, employees, and insurers to the extent the same become subject to such claim in such capacity. Myriad shall provide NYU with written notice of any claim or action within ten (10) days of its receipt thereof and shall afford NYU the right to control the defense and settlement of such claim or action. Myriad shall provide reasonable assistance to the indemnifying party in the defense of such claim or action. If the defendants in any such action include both Myriad and NYU and any party concludes that there may be legal defenses available to it which are different from, additional to, or consistent with, those available to other(s), that party shall have the right to select separate counsel to participate in the defense of such action on its behalf and such party shall thereafter bear the cost and expense of such separate defense. No party shall settle any such claim or action in a way that prejudices or adversely impacts another party to this Agreement without the prior approval of such other party (which approval shall not be unreasonably withheld).

7.4. NYU shall maintain and will continue to maintain insurance coverage appropriate to the risks involved in marketing Testing Services and will annually present evidence to Myriad that such coverage is being maintained if so requested. NYU will furnish a copy of each such insurance policy obtained and agrees that such insurance shall be in a form and in an amount reasonably acceptable to Myriad.

8. Early Termination

8.1. In the event that either party materially breaches any of the terms, conditions, or agreements contained in this Agreement to be kept, observed or performed by it, then the other party may terminate this Agreement, at its option and without prejudice to any of its other legal or equitable rights or remedies, by giving the party who committed the breach sixty (60) days notice in writing, specifying the exact nature of the breach. During such sixty (60) day period, the notified party may cure such breach and, if cured, this Agreement shall continue uninterrupted.

8.2. This Agreement will automatically terminate if NYU files for protection under applicable bankruptcy laws, becomes insolvent, makes an assignment for the benefit of creditors, appoints or suffers appointment of a receiver or trustee over its property, files a petition under any bankruptcy or insolvency act or has such petition filed against it, or if NYU is terminated or dissolved for any reason.

8.3. Upon termination of this Agreement, Myriad shall have the right to retain any sums already paid by NYU, and NYU shall pay all sums accrued hereunder which are then due.

8.4. The provisions of Sections 2.4, 4, 5 and 7 hereof shall survive the termination or expiration of this Agreement.

9. Force Majeure

If the performance of any part of this Agreement by either party, or if the obligation of either party under this Agreement is prevented, restricted, interfered with or delayed by reason of any cause beyond the reasonable control of the party liable to perform, unless conclusive evidence to the contrary is provided, the party so effected shall use its reasonable best efforts to avoid or remove such causes of non-performance and shall continue performance with the utmost dispatch whenever such causes are removed. When such circumstances arise, the parties shall discuss what, if any, modification of the terms of this Agreement may be required in order to arrive at an equitable solution.

10. Assignment

This Agreement shall be binding upon and inure to the benefit of the successors in interest of the respective parties. Neither this Agreement, nor any interest hereunder, shall be assignable by NYU without the prior written consent of Myriad.

11. Notices

Any notices required or permitted under this Agreement shall be sent by certified mail, postage prepaid, recognized courier service, or confirmed (receipt acknowledged) facsimile to the following addresses of the party:

NYU: NYU Medical Center
550 First Avenue
Room MSB136
New York, New York 10016

Myriad: Myriad Genetics, Inc.
320 Wakara Way
Salt Lake City, Utah 84108
Attention: Bill Hockett

12. Miscellaneous Provisions

12.1. This Agreement constitutes the entire agreement between the parties and supersedes all written or oral agreements or understandings concerning the subject matter thereof or in conflict with their terms.

12.2. This Agreement shall be governed by, construed in accordance with, the laws of Utah without giving effect to its principles of Conflicts of Law.

12.3. Any dispute between the parties hereunder, other than a dispute relating to patent infringement, which cannot be resolved by good faith, negotiation between the parties over a period of at least ninety (90) days shall be resolved by arbitration conducted in the English language in Salt Lake City, Utah before a panel of three arbitrators under the then current rules and procedures of the American Arbitration Association, or other rules and procedures as the parties may agree. The prevailing party in such proceeding shall be entitled to an award of its reasonable attorneys' fees and other costs, including the fees and expenses of arbitrators, provided that the same may be apportioned between the parties by the arbitrators if they determine that each party has prevailed in part. The arbitral award shall be binding and conclusive on both parties and may be enforced in any court of competent jurisdiction. Notwithstanding the foregoing, either party may, on good cause shown, seek a temporary restraining order and/or a preliminary injunction from a court of competent jurisdiction, to be effective pending the institution of the arbitration process and the deliberation and award of the arbitration panel.

12.4. No waiver by a party of any breach of this Agreement, no matter how long continuing or how often repeated, shall be deemed a waiver of any subsequent breach thereof, nor shall any delay or omission on the part of a party to exercise any right, power or privilege hereunder be deemed a waiver of such right, power or privilege.

12.5. The relationship between the parties is that of independent contractor and contractee. NYU shall not be deemed to be an agent of Myriad in connection with the exercise of any rights hereunder, and shall not have any right or authority to assume or create any obligation or responsibility on behalf of Myriad. NYU shall not use the name of Myriad in any way in connection with the performance of Research Tests or Testing Services by NYU.

12.6. In the event any portion or provision of this Agreement shall be deemed unenforceable, as written or applied, the balance of such portion or provision and the balance of this Agreement shall continue in full force and effect, as if such unenforceable portion or provision had been deleted or rendered inapplicable to the situations to which such unenforceable portion or provision cannot legally be applied.

IN WITNESS WHEREOF, the parties have executed this Agreement, individually or by their duly authorized officers, as appropriate, on the date first written above.

Myriad Genetics, Inc.	NYU Medical Center
By: ____________	By: ____________
Title: ____________	Title: ____________

APPENDIX A
PATENTS

United States Patent Number 5,693,473 - "Linked Breast and Ovarian Cancer Susceptibility Gene", Dec. 2, 1997.

United States Patent Number 5,709,999 - "Linked Breast and Ovarian Cancer Susceptibility Gene", Jan. 20, 1998.

United States Patent Number 5,710,001 - "17q-linked Breast and Ovarian Cancer Susceptibility Gene", Jan. 20, 1998.

United States Patent Number 5,747,282 - "17q-linked Breast and Ovarian Cancer Susceptibility Gene, May 5, 1998.

United States Patent Number 5,753,441 - "17q-linked Breast and Ovarian Cancer Susceptibility Gene, May 19, 1998.

[Declaration of Ellen Matloff, filed August 26, 2009] [Caption Omitted In Printing] [Exhibit 1 Omitted]

1. My name is Ellen T. Matloff. I am the Director of the Cancer Genetic Counseling Shared Resource at the Yale Cancer Center in New Haven, Connecticut. I am also a Research Scientist in the Department of Genetics at the Yale University School of Medicine.

2. I am a plaintiff in this matter. The statements herein represent my views as an individual and not those of Yale University.

3. I received my B.S. in Biology from Union College in 1991 and my M.S. in Genetic Counseling from Northwestern University in 1993. In 1996, I was certified by the American Board of Genetic Counseling. I have served as Director of the Cancer Genetic Counseling Shared Resource at the Yale Cancer Center since 1997. I have authored and co-authored published articles in the field of genetic counseling in various scientific journals including *Journal of Genetic. Counseling, The Cancer Journal from Scientific American,* and *Journal of Clinical Oncology*. A copy of my curriculum vitae is attached hereto as Exhibit 1.

4. I advise women on the risks and benefits of obtaining an analysis of their genes to determine if they have genetic mutations that correlate with an increased risk of developing breast and ovarian cancer. Specifically, the genes we most commonly analyze are known as the BRCA1 and BRCA2 genes. If I determine that such an analysis is warranted for a woman and she concurs, I arrange for the analysis and advise the woman of the significance of the

results. The only provider available to me to perform full sequencing of BRCA1 and BRCA2 is Myriad Genetics. This is not because of the high level of difficulty of the analysis, but instead it is because Myriad Genetics holds certain patents relating to BRCA1 and BRCA2 and has asserted those patents in a continuous and systematic way that has foreclosed any other provider from offering such analysis to me and my patients.

5. I am in regular contact with geneticists and lab employees. We have regularly discussed the fact that I can only use Myriad for full BRCA1 and BRCA2 testing and the harm that this situation has created. Despite the fact that many of these geneticists and their labs could perform this same testing, they have not offered such testing because it is widely known in the field that doing so would, according to Myriad, violate its patents

6. I am aware of multiple instances in which Myriad Genetics used its patents to stop genetic testing by others of the BRCA genes.

7. First, sometime in or around December 2000, I learned that the director of the Yale DNA Diagnostics Lab received a letter from Myriad Genetics directing the lab to cease BRCA1 and BRCA2 genetic testing that was being conducted in the laboratory because that testing allegedly infringed Myriad's patents. Prior to receipt of the letter, the Yale DNA Diagnostics Lab had offered BRCA1 and BRCA2 genetic analysis to me and my patients at a much lower cost of $1600. After receipt of the letter, the lab ceased to offer such genetic analysis.

8. In a separate instance in about 2005, I telephoned Myriad to inquire whether it was permissible for the Yale DNA Diagnostics Lab to perform an additional genetic screening of the BRCA genes that looked for large rearrangements. Several scientific studies had demonstrated that Myriad's full sequencing test missed large rearrangements that are also correlated with cancer risk. The Myriad Genetics representative with whom I spoke told me that he would research my question and return my call. Approximately a week later, another Myriad representative called me and said that large rearrangement testing could not be done at the DNA Diagnostics Lab because it would infringe Myriad's BRCA patents. It took Myriad approximately a year to begin offering large rearrangement testing which they called "BRCA Analysis Rearrangement Testing," or BART, even though the DNA Diagnostics Lab could have performed such additional analysis immediately. This period caused me grave concern for my patients, because large rearrangement testing is capable of identifying cancer related mutations that the basic BRCA1 and BRCA2 testing offered by Myriad does not identify.

9. It is my belief that Myriad's continuous and systematic assertion of its BRCA patents has resulted in the elimination of other genetic testing options available to me and my patients that could be cheaper, better and more appropriate. Through the BRCA patents, Myriad has exclusive access to extensive data about the women whose BRCA genes it has screened. If other researchers had access to this type of data, they could analyze it to potentially provide better information about important topics such as how the BRCA gene works, what drugs most

effectively treat women with particular BRCA mutations, and the meaning of the ambiguous test result received by some women that states "variants of unknown significance," to name a few. Because of the BRCA patents, studies that would shed light on issues like these have not been performed, and the quality of care that genetic counselors are able to provide patients has suffered.

10. If I learned that the BRCA patents owned by Myriad were invalidated, I would immediately begin to do several things that I have the capability and desire to do today, but am unable to do because of the BRCA patents.

11. First, I would send genetic samples from women who are appropriate candidates for BRCA gene analysis to laboratories other than Myriad Genetics, which would then be free to test for BRCA mutations without legal repercussion. This is not merely a hypothetical possibility, as I understand that several labs have the capability and desire to provide such service as soon as possible, including the labs of my co-plaintiffs Chung, Ledbetter and Ostrer.

12. Second, because competition would cause the cost of BRCA gene analysis to decrease if Myriad no longer monopolized the BRCA gene testing market, would order gene analysis for a larger percentage of the population of women who come to me for genetic counseling. The lower cost would be a significant factor for a large population of women, because while Myriad has a program to help cover the cost of testing for some indigent women, the program does not apply to women who either have an income that exceeds twelve thousand dollars per year or have not

been diagnosed with cancer (even though Myriad advertises their testing to women who have never had cancer). I understand from discussions I have had with personnel in the Yale Department of Genetics that the cost to provide such genetic analysis is much less than what Myriad currently charges.

13. Third, also due to the reduced cost of BRCA gene testing, I would expand the population of women whom I counsel and for whom I arrange genetic testing. Specifically, I would arrange for BRCA1 and BRCA2 testing for all women with certain types of cancer including triple negative breast cancer, medullary breast cancer, and epithelial invasive ovarian cancer, because women with these types of cancers are overrepresented in the population of women having BRCA1 and BRCA2 mutations.

14. Fourth, I would arrange for large rearrangement testing on genetic samples from all women who warrant BRCA1 and BRCA2 testing, as full sequencing does not reveal all genetic mutations along the BRCA genes. Myriad currently charges an additional $650 on top of the cost of BRCA1 and BRCA2 testing for its large rearrangement test, or BART, and most insurance companies are unwilling to pay this additional cost. I understand that several other labs have the capability and desire to provide large rearrangement testing as soon as possible, including the labs of my co-plaintiffs Chung, Ostrer and Ledbetter. Without Myriad's patent-based monopoly on BRCA testing, a decrease in the cost of such genetic testing would ensue, significantly

expanding the population of women with access to testing for large rearrangements.

15. I have the desire and capability to immediately do each of these things. The only reason I am not doing so today is because of the monopolization of the market for BRCA-related genetic testing by Myriad that has resulted from its assertion of its gene patents.

I declare, pursuant to 28 U.S.C. §1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Ellen T. Matloff

Ellen T. Matloff, M.S.

Executed on August 12, 2009

EXHIBIT 1

[EXHIBIT 1 OMITTED]

[Declaration of Patrice Fortune, filed August 26, 2009] [Caption Omitted In Printing]

1. My name is Patrice Fortune. I am a Plaintiff in the above captioned case.

2. I am a 48-year-old woman living in California.

3. After a regular screening mammogram, I was diagnosed with breast cancer in February 2009. As I was considering my treatment options, I consulted a genetic counselor. She reviewed my personal medical history and my family medical history. My maternal great-aunt and maternal great-grandmother died of breast cancer in their 40's, as well my paternal grandmother and two paternal great-aunts also had breast cancer. In addition, I have relatives who were diagnosed with other forms of cancer.

4. My genetic counselor and my physician advised me that BRCA genetic testing was appropriate for me. People with BRCA mutations are at high future risk of cancer – both breast and ovarian. Many choose to get prophylactic breast and ovarian surgery to reduce their risk of future cancers, particularly because it is difficult to screen for ovarian cancer. Also, doctors tailor screening and treatment for people who have a BRCA mutation.

5. Based on this information, I wanted to get BRCA genetic testing done as soon as possible. However, my genetic counselor told me Myriad Genetics is the only testing provider in the United States because of its patents and that it does not accept my insurance for BRCA testing. I have insurance through Medi-Cal, California's Medicaid program. I was told that even though Medi-Cal has agreed to cover some of the cost of my testing,

Myriad would refuse to process my blood sample unless I could pay out-of-pocket for the cost of the test. I am currently working in unpaid positions as I receive cancer treatment and cannot afford to pay out of pocket for a test. I looked into scholarship programs that could cover the over $3000 cost of the test, but did not identify anything that could help me.

6. Because I do not have access to BRCA full sequencing through Myriad, and because no other laboratory can offer it to me, I am not able to make the most informed decisions about the course of my current cancer treatment and about oophorectomy (surgery to remove the ovaries). I also want to let my children know about my genes. I have three children: 25-year old male/female twins and a 20-year-old son. If I get tested, they will have the information about my genes to assess their hereditary risk of cancer.

7. Another problem with the patents is that even if you can get the test through Myriad, you cannot confirm your results by getting full sequencing at another lab. I would want a verification of my results - whether they were negative or positive because I know that labs sometimes make mistakes. After I was diagnosed with breast cancer, I made sure to seek second opinions before making major choices about treatment. I would not want to opt for or against major surgery based on one test result.

8. If I learned that Myriad's patents on the BRCA1 and BRCA2 genes were invalidated, I would take action right away. I would pursue and order BRCA genetic testing through another laboratory. Without the patents, geneticists and laboratory professionals other than Myriad would be able to

offer BRCA full sequencing. I would be able to find out whether my genes have any mutations that are connected to cancer and make life decisions accordingly. This is not just speculation on my part. I understand that some of the other plaintiffs in this case, including Dr. Chung and Dr. Oster, would offer BRCA genetic testing to me if the patents were no longer a barrier. I would immediately seek testing through their laboratories if the patents were no longer in effect. I would also seek verification of my BRCA genetic test results at a second lab. I do not want to base important, life-changing medical decisions on one test.

9. The reason I do not know whether I have a BRCA genetic mutation is that the gene patents give all rights over genetic testing to the patent holder, and Myriad has refused to contract with my insurance company. Patients should not be forced to get information about their genes from only one source, at whatever cost and conditions that one source sets.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Patrice Fortune

Patrice Fortune

Executed on August 12, 2009

[Declaration of Lisbeth Ceriani, filed August 26, 2009] [Caption Omitted In Printing]

1. My name is Lisbeth Ceriani. I am a Plaintiff in the above-captioned case.

2. I am a 43-year-old woman living in Massachusetts.

3. In May 2008, when I was 42 years old, I was diagnosed with multiple tumors in both breasts (bilateral breast cancer). Soon after my diagnosis, I was told about BRCA genetic testing but the hospital staff said the test could not be done with the insurance I had.

4. During the course of my cancer treatment, I switched hospitals. My new doctor and genetic counselor advised me that my family history of breast cancer, along with the early onset of my bilateral breast cancer, suggests a possible mutation in my BRCA genes. Because people with BRCA mutations are at higher future risk of breast and ovarian cancers, and because ovarian cancer is often difficult to detect, they recommended that I obtain genetic testing to help assess my risk for ovarian cancer.

5. Based on this advice, I was determined to get BRCA genetic testing done as soon as possible. In December 2008, my doctor took a blood sample from me and sent it to Myriad Genetics for BRCA genetic testing. My doctor told me that Myriad, which is based in Utah, is the only laboratory in the United States that can do this testing. Soon after my blood was sent, a Myriad representative called me and said that the company would not process my test because

it does not accept my insurance. The only option I was given was to pay out-of-pocket.

6. I am currently insured through MassHealth, a Medicaid insurance program for low-income people in Massachusetts. Although my health insurance covers genetic testing done through contracted laboratories, Myriad refuses to contract with MassHealth. I was told that Myriad refuses to accept the $1599 reimbursement rate that MassHealth offers for the test. Myriad is the only laboratory in the U.S. that provides full BRCA gene sequencing, so it is impossible for MassHealth to "contract" with another laboratory to cover this test for its insured.

7. Therefore, the only way for me to obtain this test would be to pay Myriad for the full cost, out-of-pocket. I currently work part-time, support my young daughter as a single mother, and cannot afford to pay more than $3000 for this test. I looked into available scholarship programs to fund my test through Myriad, but did not find anything.

8. I would like to obtain genetic testing through another lab that would accept my insurance, but my genetic counselor informed me that Myriad Genetics is the only provider of this test in the United States because it owns the patents on the BRCA genes.

9. Even if I could get the test through Myriad, I could not get full sequencing done at another lab to confirm my results due to these patents. If I tested positive for a BRCA mutation, I would likely opt for an oophorectomy. But before choosing to remove my ovaries, which can have long-term consequences and side effects, I would want a verification of my results.

Second opinions become impossible when patents give exclusive rights to analyze particular genes.

10. Without the BRCA genetic test, my future is uncertain. I have undergone extensive treatment for my breast cancer, including a bilateral mastectomy, chemotherapy, radiation, and physical therapy, but I still have not been able to obtain BRCA genetic testing, the key test in determining my hereditary risk for ovarian cancer. My doctors suspect that I have a BRCA mutation and will strongly recommend a prophylactic oophorectomy to remove my ovaries if I do. However, I would not risk putting myself through such a serious surgery and accompanying side effects without validation of increased risk of ovarian cancer such as a confirmed BRCA genetic mutation.

11. If I learned that the patents on the BRCA1 and BRCA2 genes were invalidated, I would take action right away. I would pursue and order BRCA genetic testing through another laboratory. Without the patents, geneticists and laboratory professionals other than Myriad would be able to offer BRCA full sequencing. I would be able to find out whether my genes have any mutations that are connected to cancer and make life decisions accordingly. This is not just speculation on my part. I understand that some of the other plaintiffs in this case, including Dr. Chung and Dr. Ostrer, would offer BRCA genetic testing to me if the patents were no longer a barrier. I would immediately seek testing through their laboratories if the patents were no longer in effect. I would also seek verification of my BRCA genetic test results at a second lab. I do not want to base

important, life-changing medical decisions on one test.

12. More than a year has passed since I was diagnosed with cancer, and I still do not know whether I have a BRCA genetic mutation. I am in this situation because the patents over the BRCA genes allow one company to control all genetic testing, and that company has chosen not to accept my insurance. It has been and will continue to be difficult to make medical decisions without this piece of information about my genes. Also, without testing, I cannot pass on the information about my genes to my daughter. She is only 8 years old now, but when she is older, she might want to know about my genes so that she can assess her hereditary risk of cancer.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief

/s/ Lisbeth Ceriani

Lisbeth Ceriani

Executed on August 13, 2009

[Declaration of Madhuri Hegde, filed August 26, 2009] [Caption Omitted In Printing] [Exhibit 1 Omitted]

I, Madhuri Hegde, declare under penalty of perjury:

1. I am currently Senior Laboratory Director at the Emory Genetics Laboratory. I am also an Associate Professor in the Department of Human Genetics at Emory University School of Medicine and Adjunct Assistant Professor at the University of Texas M.D. Anderson Cancer Center.

2. I have a B.S. Degree in Microbiology/Genetics, a M.Sc. in Microbiology/Genetics and a PhD in Applied Science.

3. I am a member of plaintiff organizations American College of Medical Genetics (ACMG) and Association for Molecular Pathology (AMP).

4. I have received hundreds of thousands of dollars in grants for research in genetics including from the Federal government and from private foundations.

5. I have published and spoken widely on the subject of genetics. A complete copy of my curriculum vitae is attached.

6. As part of my current responsibilities, I do research on human genes. I also supervise a clinical laboratory that currently analyzes approximately 200 different genes. The lab I supervise is also supervised by plaintiff Dr. Ledbetter.

7. I would estimate we analyze approximately 60 genes every day. Analysis of genes includes sequencing the genes and then looking at the

sequence to determine if there are any variants and if those variants have clinical significance.

8. The lab that I supervise is one of the largest in the country. We have the personnel, equipment, and expertise to sequence genes including the BRCA1 and BRCA2 genes.

9. I personally sequenced the BRCA1 and BRCA2 genes while at the Auckland Hospital in New Zealand.

10. Our lab could begin sequencing BRCA1 and BRCA2 genes, and analyzing them to determine if there are variants and if those variants have clinical significance virtually immediately. The only thing that prevents us from doing so is the patents at issue in this case. I am aware that, based on these patents, other labs were sent cease-and-desist letters and that is why we do not do BRCA analysis.

11. If the patents were declared invalid, my lab would begin sequencing BRCA1 and BRCA2 genes as quickly as possible. I estimate we could begin within weeks. Even that delay is caused only because we would need to purchase certain widely-available, relatively inexpensive, and simple items to use in sequencing. We do not currently stock those items in our lab solely because we are prohibited by the patents from analyzing BRCA1 and BRCA2.

12. Our lab is not only among the largest in the country, it also utilizes the most advanced equipment and techniques. For example, we are developing high-throughput sequencing assays for rare disorders using robotics, automated sequence platforms, oligonucleotide array platforms, robotics and using predictive analysis tools and

biological testing. If we were permitted to sequence the BRCA1 and BRCA2 genes, we could do so quickly and efficiently using state-of-the art techniques.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Madhuri Hegde

Madhuri Hegde, PhD

Executed on August 13 , 2009

EXHIBIT 1

[EXHIBIT 1 OMITTED]

[Declaration of Sir John Edward Sulston, filed August 26, 2009] [Caption Omitted In Printing] [Exhibit 1 Omitted]

I, Sir John Edward Sulston declare under penalty of perjury:

1. I am Chair of the Institute for Science, Ethics and Innovation (iSEI) at the University of Manchester.

2. I received a B.A. from the University of Cambridge, UK in 1963. I received a Ph.D. from the University of Cambridge, UK in Chemistry for research in nucleotide chemistry in 1966.

3. In 1969, I joined the Medical Research Council Laboratory of Molecular Biology, Cambridge, where I researched the cellular and genetic structure of the nematode worm, *C. elegans*.

4. I became involved in genomics starting in 1983, and played a central role in both the *C. elegans* worm and human genome projects. In 1998 I and my colleagues published the sequence of the nematode worm, *C. elegans*. This was the first animal to be sequenced.

5. From 1992-2000 I served as the first Director of the Wellcome Trust Sanger Institute in Cambridgeshire. During my tenure as Director, the Institute grew from 15 staff to more than 500. Ours was the largest genome sequencing center outside of the United States and the biggest producer of genome sequence in the world. Ultimately, we were responsible for the UK's entire contribution to the international Human Genome Project — the

complete sequencing of one-third of the human genome — which was completed in 2003.

6. I was elected a Fellow of the Royal Society in 1986, and was knighted in 2001 for my contributions to genome research.

7. In 2002, I was awarded the Nobel Prize for Physiology or Medicine jointly with Sydney Brenner and Bob Horvitz, for our work in understanding the development of the nematode worm and in particular the role of "programmed cell death," or the ways in which genes regulate tissue and organ development by causing certain cells to die during the normal differentiation process.

8. I am co-author, with Georgina Ferry, of *The Common Thread: A Story of Science, Politics, Ethics and the Human Genome,* published by Bantam Press in 2002. The book tells the story of and the role of my research institute in the sequencing of the human genome, and discusses the importance of ensuring that information contained in our genome be freely available for the benefit of all.

9. A full copy of my current curriculum vitae is attached as an Exhibit.

Genes and Genetic Sequences

10. Genes and human genetic sequences are not inventions. They are naturally occurring. They are the most fundamental information about humanity, information that is — or should be — common heritage.

11. Genes are the basic units of heredity in all living organisms. A gene is a segment of DNA, the molecule that makes life possible. DNA encodes the

instructions for the development and functioning of each of our cells. As a result of the human genome project, we have come to estimate that humans have approximately 25,000 genes that make up our genome.

12. We all have essentially the same set of genes in our respective genomes, but each gene has small variations in its sequence when we compare one individual with another. The differences between us amount to only about 1 letter in 1000.

13. Scientists have long recognized the role of genes in heredity. But it wasn't until 1953 — the year of the discovery of the structure of DNA — that we came to understand how DNA played its role. This central discovery for modern biology made it immediately apparent that the structure embodies a *linear digital code*. This code — nucleic acid sequence — gets copied more or less faithfully from one generation to the next.

14. The genetic code is similar to the English alphabet, except that it consists of four letters (A, T, C, and G) rather than 26 (A through Z). A sequence of alphabetical letters can be read out as text, stored in the volatile memory of my computer, moved to a hard disc where it can survive power failure, printed out on paper, photographed, and spoken aloud, transmitted electronically, or sent to a publisher for binding in a book. Similarly, genetic sequences can also be read out into computers, and from there, we can move the resulting strings of four letters to any medium.

15. The letters of the genetic alphabet correspond to 4 chemical bases (adenine (A), thymine (T),

cytosine (C) and guanine (G)). Each gene is typically thousands of bases long, and its sequence of As, Ts, Cs and Gs usually encodes a protein. The code is a set of three-letter words — for example TTT, CAG — each of which corresponds to one of the twenty amino acids that are the building blocks of proteins. Each human gene has its place on one of the twenty-four chromosomes (numbered 1-22, plus the X and Y sex chromosomes), which together constitute the whole genome.

16. A genetic sequence is the sequence of letters of a specified section of the human genome. But beyond this, it is the *biological information itself*. Like strings of alphabetical text, the genetic sequences are the same, regardless of the medium. The physical form in which they occur is unimportant; what matters is the *informational content*. Whether the data resides in the DNA of an organism, in a computer, or as letters on a printed page, the information is the same. The entire human genome sequence consists of approximately 3 billion letters.

17. What distinguishes human genetic sequences from the English alphabet is that the information contained in the genetic sequence is a product of nature. Unlike alphabetical text, which can be arranged by my own inventive choice (and thus copyrighted), the informational content of a human gene sequence is fixed. While many inventive steps have been necessary to allow us to extract and read a genetic sequence, the ordering of the 4 letters is determined by nature.

18. The slight variations that occur among individual genomes are of great interest to some scientists, because they are thought to account for

some of the differences that we see among us. These "typos" or mutations can be in the form of the insertion or deletion of a single letter, or rearrangements, deletions or repeated segments of groups of letters. Some of these mutations have been found to have clinical significance, such as some of the mutations that have been found along the BRCA1 and BRCA2 genes.

19. Mutations are products of nature just as much as genetic sequences are. They are dictated by nature. Similarly, correlations between mutations and disease are scientific facts, or laws of nature. There is no inventive step in determining the variations, or in correlating them with medical conditions.

Genetic Sequencing

20. Genetic sequencing is the process by which one "reads", or determines the ordering of the 4 letters (A, T, C, and G) within a specified part of the genome. It is a way of transferring the DNA data contained in each and every one of our cells into a format where it can be looked at. Sequencing of a gene can easily be done by several processes that are all well known and understood by scientists, and is performed routinely in both research and clinical laboratories all over the world.

21. Progress in sequencing was slow the first two decades following the discovery of DNA. The first practical method that allowed sequences of many thousands of bases to be read out was invented by Fred Sanger and his colleagues at Cambridge England, published in 1977. It involved smashing the target DNA sample, so that many overlapping pieces

were produced, and cloning them randomly (the so-called shotgun approach). Each piece was sequenced by an ingenious method involving replication enzymes, radioactive labels and size separation of the resulting complex mixtures in an electric field. The beautiful patterns that emerge look rather like a bar code, and can be read out to yield the sequence of each piece. The individual sequences can be reassembled, using the overlaps, to yield the sequence of the entire target. In the following two decades Sanger's basic chemistry continued to be used, but many of the steps were automated, radioactive labeling was replaced with fluorescence, and the scale attainable was gradually increased. By the 1980s techniques for DNA manipulation were advanced enough so that geneticists could go fishing for genes among families of people with inherited diseases. Once they narrowed down the location of the gene, they could then try to clone the gene with a view to reading its sequence.

22. The Human Genome Project officially began in 1990, with a target of a complete human sequence by 2005. In 2000, the first human genome sequence was determined in draft form, with a more accurate and complete reference sequence achieved by 2003. Since then, progress has continued with new generations of sequencing machines following one another in rapid succession, and additional human sequences are read out routinely.

23. Our ability to sequence genes has been predicated on advances in numerous areas, including chemistry, biochemistry, instrumentation, and computing. Some of these highly inventive advances have been -- and deserved to be -- patented. These

inventions apply to *processes.* They do not apply to the data flowing through them.

24. Gene sequencing is used in diagnostic testing. A gene sequence can be examined to determine if it contains any alterations or mutations that have been associated with a particular genetic condition.

25. In order to sequence, or read a gene, we have to remove it from the cell of an organism and place it in a form so that it can be replicated outside of the body. Most commonly, we use a technique called PCR to replicate many times over small segments of the gene. Amplifying these segments allows us to read out the genetic code.

26. Promoters of gene patents argue that these steps of "isolating and purifying" a gene (removing it from the body and placing it in a form so that they can be sequenced and possibly used in other ways) is sufficient for allowing a gene to be patented. But "isolating and purifying" a gene is simply copying it into another format. It's like taking a hardback book written by someone else, publishing it in paperback and then claiming authorship because the binding is different.

27. The process of sequencing a gene does not change the informational content of that gene. The resultant sequence is informationally and functionally identical to the sequence found inside the body. The alterations or mutations in the gene that we are able to see after sequencing the gene were made by nature, not by the process of sequencing or by me or other scientists, and the effect of those alterations or mutations is dictated by nature, not by any scientist. A patent on a gene

sequence and any mutations of that gene gives a monopoly over this information, regardless of the person from whom the gene is taken or the sequencing process that is used.

Information Sharing in Genomic Research

28. From the point of view of scientific research, human genetic sequences are as basic as you can get in terms of biological information. They are as basic as the elements in the periodic table. Patenting a gene or genetic sequence impedes scientific progress much the same way that patenting a naturally occurring element such as oxygen or gold would impede science.

29. From the very beginning of the Human Genome Project, most scientists and even some private companies recognized the importance of keeping the genome freely available to all. In 1994, the pharmaceutical company Merck funded a massive drive to generate genetic sequences and place them into public databases. By doing this Merck not only gave the entire research community, public and private, free access to valuable genomic data; it also made those sequences much more difficult to patent.

30. In November 1995, a team of researchers at the United Kingdom-based Institute of Cancer Research (ICR) led by Michael Stratton (who went on to become the head of the Cancer Genome Project at the Sanger Centre) found a mutation in some of their breast cancer patients, which appeared to lie in BRCA2. Michael Stratton was collaborating with Mark Skolnick at the University of Utah. He ended the collaboration when he learned from Skolnick that

the company he had started, Myriad Genetics. planned to patent the gene and own exclusive rights to exploit it both for diagnosis and therapy if the collaboration were to find and clone the BRCA2 gene. Shortly thereafter BRCA2 was sequenced by the Sanger Centre. Over the next two weeks, the ICR team confirmed their results and identified five additional mutations. But the day before their findings were published, Mark Skolnick filed a patent application for BRCA2.

31. Myriad used its patent applications to claim rights over the entire BRCA2 gene, including the mutations that had been identified by ICR. Myriad has since claimed proprietary rights for all diagnostic testing for the BRCA genes. One of their tests focuses on one of the mutations discovered by the ICR team that is commonly found among Ashkenazi Jews from central and eastern Europe. Thus, by having a patent on the gene as a whole, Myriad was able to claim scientific findings made by others. Myriad has benefited directly from the work of the international scientific community, while their practices have driven up health care costs and impeded further research on these genes that might lead to future therapies.

32. Michael Stratton concluded from this experience that the only way he could protect his team's discovery from commercial exploitation by others was to patent it himself. As a result, the Institute took out one patent on the first mutation as soon as it was discovered, and another later covering more mutations.

33. This experience with Myriad in the mid-nineties prompted some of us to seek a commitment

from the international sequencing community that genomic information would be made publicly available and not patented. In 1996, we organized an international meeting in Bermuda to overcome rivalries in the large international consortium and ensure that data was released in a timely fashion. The meeting was attended by 50 scientists from around the world, and established the so-called Bermuda principles: public sequencing labs would release data within 24 hours of its collection, by deposit into a public database, and would not take out patents on it. We stated: "All human genomic sequence information should be freely available and in the public domain in order to encourage research and development and to maximise its benefit to society."

34. Although the genome as a whole is in the public domain, patents are now issued or pending on some 25% of human genes. These patents stand in sharp contrast to the tenor of the Bermuda meeting and threaten to undermine scientific and medical progress.

35. There is still much to learn about the products of our genes — what they look like, when or where they are produced, and how they interact with one another. In order to translate this information into medical advances, this basic data must be freely available to everyone to interpret, update and share. The situation is too complex for a piecemeal approach, in which a single entity holds the key to any given gene.

36. Data sharing is also key to the future of genetic discoveries and bioinformatics. This is because a lot of value comes from comparing one

sequence with another, both within a genome and between genomes. Many genomes other than human have now been sequenced in whole or part, and much of this information is available on the web for all to use. A remarkable finding from all this data is the tremendous unity of life at the sequence level, incidentally confirming the fact of evolution in a way that is complementary to relationships deduced from the physical appearance of organisms. It turns out for example that half of our human genes have recognizable counterparts in insects.

37. Patents on human genes and genetic sequences are deleterious to the practice of science. Because gene patents tend to cover all uses of that sequence, they are a disincentive to further research on those genes. Patents on genes damage accessibility to this most basic information and discourage scientific communication and data sharing.

38. Patents on human genes will be deleterious to unraveling their role in medical conditions. As we move into an era where the sequencing of the genes of an individual is more efficient than obtaining the sequence for a gene or two, scientists will discover individual variations in genes whether they are patented or not. Free sharing of this information will be vital in understanding the role of these variations in the human disease and other traits.

I declare, pursuant to 28 U.S.C. §1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ John E. Sulston

John E. Sulston, Ph.D

Executed on 17 August, 2009

EXHIBIT 1

[EXHIBIT 1 OMITTED]

[Declaration of Mildred Cho, filed August 26, 2009] [Caption Omitted In Printing] [Exhibit 1 Omitted]

I, MILDRED CHO, PhD, certify under penalty of perjury that the following is true and correct:

1. I am currently the Associate Director of the Stanford Center for Biomedical Ethics and Associate Professor in the Stanford University Department of Pediatrics, Division of Medical Genetics. I am also the Director of the Center for Integration of Research on Ethics and Genetics, and Principal Investigator of the grant that supports this National Institutes of Health Center for Excellence in Ethical, Legal, and Social Implications (ELSI) Research, which was established to investigate the ELSI of genetic research. I teach courses on the ethics of biomedical research and conduct research on ethical issues in the conduct and application of biomedical research, especially those arising in the field of genetics.

2. I submit this certification in support of Plaintiffs' motion for summary judgment. Based on my research and expertise, in the case of clinical genetic tests, patents on such tests inhibit scientific research, discourage application of research to clinical practice, and are not required to spur innovation. Thus, patents on genetic tests are inhibitory to access to clinical diagnosis and potentially harm patients.

3. I have a BS degree from the Massachusetts Institute of Technology in Life Sciences, a PhD from Stanford University in Pharmacology, and post-doctoral training in health policy from the University of California, San Francisco and from the Center for

Health Care Evaluation of the Palo Alto Veterans Affairs Medical Center. Prior to my appointment at Stanford, I was Assistant Professor of Bioethics at the University of Pennsylvania Center for Bioethics.

4. I am a member of several professional organizations, including the American Society of Human Genetics, the American College of Medical Genetics, and the American Society for Bioethics and Humanities.

5. I am, and have served as, an advisor to research and development programs in the United States and other countries regarding the conduct and commercialization of biomedical and genetic research. These institutions include the National Human Genome Research Institute, the United Kingdom Biobank, the Wellcome Trust, Genome Canada, the World Health Organization, and the Organization for Economic Cooperation and Development.

6. I have conducted empirical research on the effects of commercialization of academic research. A complete list of my publications is contained in my curriculum vitae, attached as an Exhibit.

7. In 1998 and 1999, I conducted preliminary studies to examine the effects of gene patents on laboratories that conduct clinical genetic tests and to examine the nature of the patents themselves and how and whether they were licensed.

8. In 2000, I received a grant from the National Human Genome Research Institute of the U.S. National Institutes of Health (Grant # 1 R01 HG02034) to conduct a series of studies on the effects

of U.S. gene patents and licensing practices on genetic research and clinical practice.

Effects of gene patents

9. As part of our NHGRI-funded grant, we performed a systematic telephone survey between July and September 2001 of all laboratory directors in the United States who were likely to be conducting genetic tests. These directors included members of the Association for Molecular Pathology (an organization of professionals who conduct genetic testing in the United States, and a plaintiff in this case), and directors of U.S. laboratories who were listed on the GeneTests.org website (an online clearinghouse of laboratories worldwide that conduct clinical genetic tests).

10. We found that over half of the lab directors who responded to our survey (53%) reported deciding not to develop a new clinical genetic test because of a gene patent or license. Two-thirds (67%) of respondents believed that gene patents resulted in a decreased ability to do research, whereas only 3.4% of respondents believed that gene patents increased the ability to do research. Another study of members of the American Society of Human Genetics reported similar results, finding that 46% of respondents felt that patents have delayed or limited their research (Rabino, I., 2002, How human geneticists in US view commercialization of the Human Genome Project. *Nature Genetics* 29:15-16).

11. We also found that 25% of respondents reported that they had stopped performing a clinical genetic test because of a gene patent or license (Cho, MK *et al.*, 2003, Effects of Patents and Licenses on

the Provision of Clinical Genetic Testing Services, *Journal of Molecular Diagnostics* vol. 5, no. 1, pages 3-8.)

12. We contacted all 211 laboratory directors identified in June 2001 and received responses from 132 (63%). Of these, 10 were excluded because they did not perform DNA-based genetic testing. Respondents did not differ in a statistically significant way from nonrespondents in the likelihood of being from a for-profit or not-for-profit institution (P=0.37).

13. The majority of respondents (65%) said that their laboratories had been contacted by a patent or license holder regarding the laboratory's potential infringement of a patent by performance of a genetic test. These notifications were regarding the conduct of several genetic tests, including of BRCA1/BRCA2 genes.

14. We asked the 25% of laboratory directors reporting that they decided to cease offering a clinical test because of a patent or license which tests they ceased to perform. These laboratories reported ceasing to perform 12 clinical tests, including the BRCA1 and BRCA2 tests for hereditary breast and ovarian cancer.

15. To put these 12 tests into context, we found that 461 genetic tests were offered in the GeneTests database as a clinical service, the vast majority of which (394) were for rare disorders and performed by 10 or fewer laboratories (of the 133 laboratories identified in GeneTests who conduct genetic tests). However, all of the 12 tests that laboratories had stopped performing were offered by 11 or more

laboratories. This finding suggests that patents affect laboratories that test for and patients who have more common conditions.

16. A total of 9 respondents reported that they had stopped performing tests for BRCA1 and BRCA2 because of patents. More laboratories had stopped performing BRCA1 and BRCA2 tests than any other test, with the exception of Apolipoprotein E (Apo E). Nine respondents reported having stopped performing tests for Apo E.

Role of patents in innovation and commercialization

17. Other studies that we conducted indicate that gene patents are not required to bring discoveries into commercial production or clinical practice, and that gene patents are also not required as incentives to spur the initial discoveries because the majority of patented gene discoveries were supported by the federal government.

18. We conducted a study of patenting and licensing of a specific genetic test for hemochromatosis, a common condition affecting 1 in 200 to 1 in 300 people of Northern European descent, with a carrier frequency of up to 1 in 10.

19. We identified 117 laboratories through GeneTests and the Association for Molecular Pathology tests directory and 11 additional laboratories through snowball sampling for a total comprehensive sample of 128 laboratories conducting hemochromatosis testing in the U.S. in 1999. We received responses from 119 laboratories (93%).

20. Thirty-one laboratories (26%) reported that they had not developed and were not performing the

hemochromatosis test, and 5 (4%) had stopped performing the test, with 32 of 36 citing patents as a reason. Thus, as we found for other genetic tests, the existence of a patent had a significant impact on laboratories that could have offered the hemochromatosis test.

21. While awareness of a patent on the hemochromatosis test appeared to inhibit the adoption by clinical laboratories, patents were not necessary for rapid introduction of the test. Patents on the test were filed in mid-1995 through mid-1996, and the first publication of the discovery of the hemochromatosis gene appeared in August, 1996. Laboratories immediately began offering clinical genetic tests for hemochromatosis, with the mean time from publication to adoption (by laboratories represented in our survey) of 14 months. Indeed, 60% (35 of 58 performing hemochromatosis testing at the time of our survey) reported introducing the clinical test *before* the first patent was issued in January 1998.

22. Another study of gene patents issued in the U.S. on genetic diagnostics showed that two-thirds (67%) were for discoveries funded by the US government (Schissel, A., Merz, JF., Cho, MK., 1999. Survey confirms fears about licensing of genetic tests. *Nature* 402:118.) This is another indication that patents themselves are not necessary for initial discoveries relevant to clinical genetic diagnostics. This preliminary study identified 33 U.S. patents issued in 1991-1997 that broadly covered the diagnosis of human genetic disorders held by U.S. institutions and that were not expired. Of these 33

patents, 22 were funded at least in part by the U.S. government.

23. Therefore, perhaps unlike other discoveries such as chemical compounds that have pharmaceutical potential, and that require lengthy and expensive further development in order to become commercially available and accessible to patients, in the case of genetic findings relevant to clinical tests, the exclusivity offered by patents is not necessary to incent either the initial discovery or its clinical application.

Conclusions

24. Thus, our results provide evidence that patents on genes used for clinical diagnostics inhibit the conduct of research to further the development of improvements to genetic tests. Our findings also provide evidence that such patents inhibit clinical diagnostic laboratories from providing clinical tests and services.

25. We have also found evidence that, at least for gene discoveries relevant to clinical diagnostics, patents are not necessary to incent either the research on initial discoveries or the development of clinical applications and commercializable products.

I declare, pursuant to 28 U.S.C. §1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Mildred Cho

Mildred Cho, Ph.D.

Executed on August 17, 2009

[Declaration of Judy Norsigian, filed August 26, 2009] [Caption Omitted In Printing]

1. My name is Judy Norsigian. I am Executive Director of the Boston Women's Health Book Collective ("BWHBC"). BWHBC is a Plaintiff in the above-captioned case.

2. The Boston Women's Health Book Collective, more commonly known as Our Bodies Ourselves, is a nonprofit, public interest women's health education, advocacy, and consulting organization.

3. Our mission is to provide truthful, accessible, research-based information about women's health and sexuality. We vigorously advocate for women's health by challenging the institutions and systems that block women from full control over our bodies and inspiring and empowering women to become engaged in health policy.

4. Since 1970, we have authored eight editions of *Our Bodies Ourselves* (published by Simon and Schuster since 1973). This book has become a classic resource educating women about health, sexuality, and reproduction. The eighth edition was published in 2005. We have written additional books, have distributed more than 10,000 books and materials free of charge worldwide, and currently facilitate translation and adaptation projects in such countries as India/Bangladesh, Israel, Turkey, Nepal, Nigeria, and Tanzania. Similar projects completed in other countries (for example, Russia, Albania, South Korea, Serbia, and Thailand) are described at our website, www.ourbodiesourselves.org. In recent years, we launched a blog, which currently is read by several thousand people on a daily basis.

5. This case seeks to invalidate patents that have been granted on the BRCA1 and BRCA2 genes. That goal is completely in line with the mission of BWHBC. Two of our core principles are: women can become their own health experts, particularly through discussing issues of health and sexuality with each other; and health consumers have a right to know about controversies surrounding medical practice and about where consensus among medical experts may be forming.

6. The BRCA gene patents contradict these principles. The gene patents give the patentholder the right to control all testing and research done on the genes — in effect, the right to control the information that is learned about the BRCA1/2 genes. This is harmful to women's health. Women and their doctors should have access to information about a particular patient's genes, as well as aggregated data for research purposes. Instead, women have been unable to afford BRCA genetic testing because of the high cost of the test and they also have access only to the testing the patentholder allows. In the U.S., that means that patients can get BRCA1/2 full sequencing done only through Myriad Genetics. As we reported on our website in March 2006, Myriad's standard full sequencing test was shown to yield a 12% false negative rate in high-risk women in one major scientific study.[1] BWHBC cannot advocate for researchers and clinicians to perform BRCA1 and BRCA2 related activities, even

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[1] Available at www.ourbodiesourselves.org/book/news.asp?newsID=32.

when the activities might be aimed at creating new testing methods that Myriad Genetics does not offer or performing testing at a lower price. We cannot refer readers to or publicize full gene sequencing services at laboratories other than or in addition to Myriad Genetics.

7. These broad patents — which cover the actual BRCA1/2 genetic sequences, mutations, and their correlations with hereditary breast and ovarian cancers -- are a barrier to a woman's ability to know about her body and make informed health decisions. A hypothetical, but not unrealistic, example illustrates the extent to which the patents restrict a woman's access to information about the genes in her own body: Imagine a woman who has an extensive family history of breast cancer and has been diagnosed with cancer wants to learn about her hereditary risk; she is a trained laboratory professional with the resources and ability to conduct a test to examine a blood sample for mutations along the BRCA1/2 genes; and yet, she cannot draw her own blood and run the test without technically violating the patents. That is because the patents are on the genes and the information they hold, including her own genetic information.

8. BWHBC's work has been frustrated by the BRCA1/2 gene patents and Myriad Genetics' exclusive control over genetic testing. We have had to use our scarce resources to identify and address the problems that result, including staff time for investigating, writing and publishing articles about these problems and engaging in advocacy on these issues. For example, I wrote a letter in May 2007 on behalf of Our Bodies Ourselves in support of a

federal bill that would limit patenting of human genes.[2] We also have voiced our concerns about Myriad's direct to consumer marketing practices.[3] And because the patents extend over the correlation between mutations and hereditary risk of cancer, any publication of that correlation by BWHBC could be alleged to induce patent infringement, even though one of BWHBC's main purposes is to educate the public about women's health, including breast and ovarian health. Invalidation of the patents would advance our mission of ensuring that women have full access to truthful information about their bodies and health.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of nay knowledge and belief.

/s/ Judy Norsigian

Judy Norsigian

Executed on August 17, 2009

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[2] Available at http://becerra.house.gov/HoR/CA31/Issues/OurBodiesOurselvesLetter.htm.

[3] See, for example, www.ourbodiesourselves.org/book/companion.asp?id=28&compID=27, and www.ourbodiesourblog.org/blog/2007/09/selling-women-fear-through-genetic-testing-ad.

[Declaration of Haig Kazazian, Jr., M.D., filed August 26, 2009] [Caption Omitted In Printing] [Exhibit 1 Omitted]

1. My name is Haig H. Kazazian, Jr.. I am the Seymour Gray Professor of Molecular Medicine in the Department of Genetics at the University of Pennsylvania School of Medicine as well as co-Director of the University of Pennsylvania Genetic Diagnostic Laboratory. I am one of the plaintiffs in this case.

2. I received my medical degree from Johns Hopkins University in 1962. I have been the Seymour Gray Professor of Medicine in the Department of Genetics at the University of Pennsylvania School of Medicine since 1994, and I was chair of the Department from 1994 to 2006. From 1989 to 1994 I was a Professor of Medicine, Pediatrics, Obstetrics and Gynecology, and Biology at The Johns Hopkins University School of Medicine, where I directed the Center for Medical Genetics from 1989 to 1993. I received my board certification in Molecular Genetics from the American Board of Medical Genetics in 1993. I am a member of the American Board of Medical Genetics and was president of the Board from 1999-2000. I am on the editorial boards of *Human Mutation, Human Genetics, Somatic Cell and Molecular Biology,* and *Mobile DNA.* A copy of my curriculum vitae is attached hereto as Exhibit 1.

3. I have directed the Genetic Diagnostic Laboratory since 1995 along with my colleague Dr. Arupa Ganguly. Through the Genetic Diagnostic Laboratory, Dr. Ganguly and I provide state-of-the-

art DNA-based diagnostic testing for a variety of genetic conditions and diseases, as well as prenatal and predictive testing and genetic counseling services. Prior to 1995, I started the first clinical gene diagnostic lab at Johns Hopkins in 1978.

4. Sometime around 1996, after the BRCA1 gene was identified, Dr. Ganguly and I designed tests to screen the BRCA1 gene in our lab. Dr. Ganguly made considerable effort over roughly a six-month period to set up these tests. By roughly the middle of 1996, we were providing BRCA1 genetic testing services to approximately 500 women per year. We designed and provided a similar test for the BRCA2 gene by late 1996, after that genetic sequence was identified.

5. Dr. Ganguly and I were forced to stop providing our BRCA1 and BRCA2 testing services in 1999 after we were accused by Myriad Genetics of infringing their BRCA related patents. The details of the communications comprising that accusation, as I recall them, are as follows.

6. Sometime in the late 1990s, I had a dinner meeting with Dr. Mark Skolnick, who is one of the named inventors of Myriad's BRCA patents as well as Chief Science officer at Myriad. The purpose of our dinner meeting, which took place in New York City, did not relate to BRCA research. However, during dinner, Mark told me that Myriad planned to stop the BRCA testing activity that Dr. Ganguly and I were performing. I understood from the context of our conversation that the Myriad BRCA patents were his basis for objecting to our testing.

7. About a month or two after my dinner meeting with Dr. Skolnick, either I or the University's

General Counsel, Mr. Robert Terrell, received a letter from a Myriad representative claiming that the BRCA testing activity we were conducting at our Genetic Diagnostic Laboratory infringed Myriad's BRCA patents and asking us to cease the activity. When I spoke to Mr. Terrell about the letter, he communicated that the University would not be contesting the accusation and advised us to stop our BRCA testing. Dr. Ganguly and I stopped performing BRCA screening at that time and have not resumed since.

8. At the time we were forced to stop offering BRCA genetic services, we were charging patients less than Myriad was charging. If we, or another laboratory, were to begin offering such genetic testing again, I believe that it would be offered at a price significantly lower than Myriad's current pricing for the same or similar testing.

9. Further, the test we had developed to screen for BRCA mutations was not the same kind of test that Myriad was using. While they were similar, ours started with a screening of all the exons by a method Dr. Ganguly had developed and that was followed by sequencing of any abnormal exon found by the first procedure. Their method went directly to sequencing all the exons. Regardless, Myriad accused us of patent infringement because we were analyzing the genes, not because we were using a particular test that had been developed by Myriad.

10. Before we were forced to stop offering BRCA genetic testing, we were the only laboratory in the nation providing BRCA genetic testing to patients other than Myriad Genetics. Since the time we ceased offering our BRCA genetic testing services, no

other laboratory in the nation has offered BRCA genetic testing to patients other than Myriad. There may be a couple of isolated university affiliated labs that are permitted to perform a specific test for particular mutations for their own patients, but they are not allowed to perform a full sequencing test or a test for large rearrangements, or to offer their services to the public at large.

11. Our laboratory currently has all of the technological capability necessary to begin performing BRCA testing again. If Dr. Ganguly and I were to learn that Myriad's BRCA patents no longer had legal effect and we decided to resume BRCA testing, we would be able to do so within a matter of a few weeks.

I declare, pursuant to 28 U.S.C. §1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Haig H. Kazazian

Haig H. Kazazian, Jr.

Executed on August 17, 2009

EXHIBIT 1

[EXHIBIT 1 OMITTED]

[Declaration of Michael S. Watson, filed August 26, 2009] [Caption Omitted In Printing]

I, Michael S. Watson, declare under penalty of perjury:

1. I am the Executive Director of the American College of Medical Genetics (ACMG), one of the plaintiffs in this case.

2. ACMG is a private, non-profit voluntary organization of clinical and laboratory geneticists. The Fellows of the ACMG are doctoral level medical geneticists and other physicians involved in the practice of medical genetics. With more than 1300 members, the ACMG's mission is to improve health through the practice of Medical Genetics. In order to fulfill this mission, the ACMG strives to 1) define and promote excellence in medical genetics practice and the integration of translational research into practice; 2) promote and provide medical genetics education; 3) increase access to medical genetics services and integrate genetics into patient care; and 4) advocate for and represent providers of medical genetics services and their patients.

3. ACMG has brought this case on behalf of its members some of whom are ready, willing, and able to engage in research and clinical practice involving the BRCA1 and BRCA2 genes if the patents are invalidated. One or more ACMG members are submitting separate declarations concerning their ability to engage in research and clinical practice now prohibited by the patents.

4. This case seeks to invalidate broad gene patents such as those listed in the Complaint. As the recitation of our purposes in paragraph 2 indicate,

that interest is germane to the purposes of ACMG. One of ACMG's purposes is to enable its members to advance human understanding of genes. The patent impedes that purpose. Another purpose of ACMG is to ensure that the patients for whom our members are responsible receive high quality, accurate tests when necessary. The patent impedes that purpose.

5. Over the years, ACMG has issued or signed statements concerning gene patents as a regular part of its mission. See e.g. http://www.acmg.net/StaticContent/StaticPages/Gene_Patents.pdf (visited August 3, 2009).

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Michael S. Watson

Michael S. Watson

Executive Director, ACMG

Executed on August 18, 2009

[Declaration of Arupa Ganguly, filed August 26, 2009] [Caption Omitted In Printing] [Exhibit 1 Omitted]

1. My name is Arupa Ganguly. I am an Associate Professor in the Department of Genetics at the Hospital of the University of Pennsylvania, University of Pennsylvania School of Medicine as well as Director of the University of Pennsylvania Genetic Diagnostic Laboratory.

2. I received my Ph.D. in Biophysics from the University of Calcutta in 1984. I completed a post doctoral fellowship at Thomas Jefferson University in 1990. I have been Associate Professor of Genetics at the University of Pennsylvania School of Medicine since 2003, previous to which I was Assistant Professor of Genetics since 1996. I have been the Director of the R&D Genetic Diagnostic Laboratory at the University of Pennsylvania since 1995. I also speak and write frequently on genetics related topics. Articles I have authored or co-authored have appeared in *American Journal of Medical Genetics, Molecular Genetics & Metabolism*, and *Human Genetics*. A copy of my curriculum vitae is attached hereto as Exhibit 1.

3. In the R&D division of the Genetic Diagnostic Laboratory, my work included comprehensive screening of both the BRCA1 and BRCA2 genes. My BRCA screening was for both research and clinical purposes and at some points my lab was the only other provider of BRCA testing services that included the full screening of the BRCA1 gene in the nation other than the defendant, Myriad Genetics.

However, in the late 1990s I was compelled to stop all of my BRCA screening after we received an extensive series of communications from Myriad in which Myriad accused my lab of violating its BRCA related patents (the same patents involved in this case). The details of the communications we had with Myriad about their patents and my lab's activities are as follows.

5. On or about May 29, 1998, my colleague and co-Director of the Genetic Diagnostic Laboratory, Haig Kazazian, who is also a co-plaintiff with me in this case, received a letter from William A. Hockett, Director of Corporate Communications for Myriad. A copy of this letter is attached hereto as Exhibit 2. The letter stated that Myriad knew we were providing diagnostic testing services for BRCA1 and asserted that Myriad is "the patent holder for the BRCA1 gene." The letter specified that Myriad had five patents on BRCA1, that covered, amongst other things, "composition of matter covering the BRCA1 gene [and] any fragments of the BRCA I gene." The letter then stated that Myriad was offering a collaboration license to the University of Pennsylvania Medical Center, but only for single mutation tests and multiple mutation panels up to four mutations to allow for testing [of] patients of Ashkenazi Jewish descent." Thus, the license offered was of very limited scope, as it would not allow us to provide complete diagnostic testing services for BRCA1, or comprehensive research on the BRCA1 gene which we had been doing at the lab.

6. Then, on or about August 26, 1998, Dr. Kazazian received another letter, this time from George A. Riley of O'Melveny & Myers, LLP, who

claimed to be representing Myriad Genetics. A copy of this letter is attached hereto as Exhibit 3. This letter again stated that, "Myriad is the owner of United States Patents Nos. 5,693,473; 5,709,999; 5,710,001; 5,747,282; and 5,753,441 covering, among other things, the BRCA1 gene sequence, mutations in the BRCA1 gene, ... and methods for detecting alterations in the BRCA1 sequence." The letter continued to assert that, "It has come to Myriad's attention that you are engaged in commercial testing activities that infringe Myriad's patents." The letter then demanded that, "you should cease all infringing testing activity."

7. On or about June 10, 1999, the University of Pennsylvania general counsel, Robert Terrell, received a letter from Myriad Genetics' General Counsel, Christopher Wight. A copy of this letter is attached hereto as Exhibit 4. This letter stated, "It has come to our attention that Dr. Haig H. Kazazaian, Jr. of the University of Pennsylvania is continuing to willfully engage in commercial BRCA 1 and BRCA2 genetic testing activities, in violation of the University of Pennsylvania's previous assurances that such commercial testing activities would be discontinued." The letter continued to assert that, "Dr. Kazazian's commercial testing activities infringe one or more of the following U.S. Patents owned by Myriad Genetics: 5,693,473; 5,709,999; 5,710,001; 5,747,282; 5,753,441, and 5,837,492." The letter then demanded that, "the University of Pennsylvania discontinue offering and conducting all such commercial genetic testing services," and requested that Myriad be provided with, "written assurances that the University of Pennsylvania has stopped providing the infringing tests."

8. On September 10, 1999, Robert Terrell responded to Christopher Wight by letter. Both Dr. Kazazian and I were copied on this letter, a copy of which is attached hereto as Exhibit 5. In the letter, Mr. Terrell admits that our lab's activities after receipt of the August 26, 1998, letter from George Riley had been modified to comply with Myriad's demands set forth in that letter. The letter also states that, "the University agrees that it will not accept samples for BRCA1 research testing from third parties."

9. On or about September 22, 1999, Robert Terrell received a response from Christopher Wight. A copy of this letter is attached hereto as Exhibit 6. In this letter, Wight reiterated Myriad's belief that the genetic testing activities being performed at the University of Pennsylvania infringed Myriad's patents and again demanding written assurance that such activities had stopped.

10. As a result of the series of communications described above, I was compelled to cease all BRCA1 and BRCA2 testing, whether for research or clinical purposes. While I still have the capability to do such services and the desire to consider offering them again, I feel unable to do so because of the past patent assertion by Myriad against my work. Thus, I have moved on to other areas of investigation.

11. I am aware of at least two other instances in which Myriad asserted that BRCA genetic testing activity infringed its patents.

12. In 1998, my colleague Barbara Weber was the principal investigator on a project sponsored by the National Cancer Institute ("NCI") called the Cancer

Genetics Network Project. The project involved eight cancer centers across the United States. As a Co-Principal Investigator of that project, I provided BRCA1 and BRCA2 screening to Dr. Weber's research participants at relatively low cost. On or about September 15, 1998, the President of Myriad, Gregory Critchfield, sent a letter to Susan Nayfield of the NCI. A copy of that letter is attached hereto as Exhibit 7. In the letter, Myriad's President addressed "concerns that have arisen about how Myriad Genetics' BRCA1 patent position might impact on research efforts sponsored by the National Cancer Institute." The letter continued to say that Myriad would offer licenses to third-party laboratories performing BRCA testing, inferring that such licenses were required to avoid such patent based "concerns." At the time, mine was the only such third-party laboratory offering such services, so the letter was a direct attack on my activities. In essence, Myriad was telling Dr. Weber that my BRCA related activities in support of her project infringed their patents. As a result of that letter, I stopped performing BRCA testing for the Cancer Genetics Network Project.

13. Further, Georgetown University was one of the cancer centers that participated in the Cancer Genetics Network Project. As such, Georgetown had also been sending genetic samples of research participants to my laboratory for BRCA1 and BRCA2 screening. On or about September 2, 1999, a Myriad representative sent a letter to the Georgetown laboratory demanding that Georgetown no longer send genetic samples to my laboratory for testing, because such activity, in their opinion, infringed Myriad's BRCA patents. As a result of that letter,

Georgetown stopped sending samples to my lab for BRCA screening.

14. If Myriad's BRCA patents were invalidated, I would immediately consider resuming BRCA testing in my laboratory. I currently possess all of the resources and technological capability necessary to do so. I would resume BRCA testing to advance research and/or to offer what I believe is an important service to the public, including at minimum the individual women who are co-plaintiffs with me in this case. If I decided to resume offering such services, I could do so within a matter of weeks. The only thing preventing me from resuming BRCA testing in my lab is the assertion of the BRCA related patents by Myriad and I have the earnest desire to immediately consider doing so.

I declare, pursuant to 28 U.S.C, §1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Arupa Ganguly

Arupa Ganguly, Ph.D.

Executed on August 18, 2009

EXHIBIT 1

[EXHIBIT 1 OMITTED]

EXHIBIT 2

Myriad

May 29, 1998

Haig H. Kazazian, Jr., M.D., F.A.C.M.G.
Director, Genetic Diagnostic Laboratory
University of Pennsylvania Medical Center
415 Curie Boulevard, Rm. 475 CRB
Philadelphia, PA 19104-6145

Dear Dr. Kazazian:

I understand that you are currently providing diagnostic testing services for BRCA1. Myriad Genetics, as the patent holder for the BRCA1 gene, is making a collaborative license available to select institutions. Accordingly, I have enclosed Myriad's Standard Collaboration Agreement relating to BRCA1 testing.

Myriad Genetics has been awarded five US patents covering BRCA1. These patents cover (i) 47 individual mutations including the BRCA I mutations common in the Ashkenazi Jewish population (185delAG, 5382insC); (ii) predisposition diagnostic testing for these deleterious mutations; (iii) diagnostic testing of tumor samples for alterations in BRCA1; (iv) composition of matter covering the BRCA1 gene, any fragments of the BRCA1 gene and primers of the BRCA1 gene; and (v) use of the BRCA1 gene in diagnostic testing for breast and ovarian cancer susceptibility.

For a limited period of time, Myriad Genetics is going to offer collaboration licenses to select

Universities, laboratories and cancer centers to perform BRCA1 testing using the Company's patented mutations and technology. The Company is pleased to offer such a collaboration license to the University of Pennsylvania Medical Center. The Agreement covers single mutation tests and multiple mutation panels (up to four mutations) to allow for testing patients of Ashkenazi Jewish descent. The Agreement specifies a modest fee per test without any up-front license fee or minimum annual royalty.

If you have any questions or comments concerning this agreement, please call me at the number listed below. I look forward to your reply.

Yours sincerely,

/s/ William A. Hockett

William A. Hockett
Director of Corporate Communications
Phone: (801) 584-3504
Fax: (801) 584-3518
email: bhockett@myriad.com

COLLABORATION AGREEMENT

This Non-Exclusive Collaboration Agreement (hereinafter "Agreement"), effective the _ day of __ , 1998 is between Myriad Genetics, Inc. (hereinafter referred to as "Myriad"), having a business address at 320 Wakara Way, Salt Lake City, Utah 84108, and the University of Pennsylvania Medical Center (hereinafter referred to as "University"), located at 415 Curie Boulevard, Rm. 475 CRB, Philadelphia, Pennsylvania 19104-6145.

WHEREAS, Myriad holds rights to certain Patents relating to the human BRCA1 gene, which Patents are described in Appendix A, attached hereto; and

WHEREAS, University desires to receive a non-exclusive license to utilize said Patents, in order to develop, and seek and obtain regulatory approval for, certain testing services to be performed by University; and

WHEREAS, Myriad and University desire to collaborate on certain ongoing research activities concerning the human BRCA1 gene and predisposition to breast or ovarian cancer.

NOW, THEREFORE, the parties hereto, intending to be legally bound hereby, agree as follows:

1. Definitions.

1.1. An "Affiliate" is any person, corporation, firm, partnership or entity, whether *de jure* or *de facto,* which directly or indirectly owns, is owned by, or is under the common ownership of a party to this Agreement to the extent of at least fifty percent

(50%) of the equity of the owned entity, having the power to vote on or direct the affairs of the owned entity, and any person, corporation, firm, partnership, or other entity actually controlled by, controlling or under common control with a party to this Agreement.

1.2."Patents" means those patents or patent applications listed on Appendix A; and any patents or patent applications which claim the BRCA gene or uses of the BRCA1 gene, which are owned by Myriad or are subject to assignment or license, in whole or in part, to Myriad. Included within the definition of Patents are any continuations, continuations-in-part, divisions, patents of addition, reissues, renewals or extensions thereof.

1.3. "Research Tests" shall mean tests under an IRB approved protocol for the presence or absence of BRCA1 mutations for the purposes of furthering non-commercial research programs, the results of which are not provided to the patient and for which no money is received from the patient or the patient's insurance.

1.4 "Testing Service" shall mean medical laboratory testing under an IRB approved protocol for the presence or absence of BRCA1 mutations for the purpose of determining or predicting predisposition to, or assessing the risk of breast or ovarian cancer in humans. For the purposes of this Agreement, Testing Services shall include only mutation-specific screening tests which are performed to detect a maximum of four mutations per test.

2. Grant of Rights and Collaborative Activities.

2.1. Myriad hereby grants University the non-exclusive right under the Patents to develop and use Research Tests and to develop, market, use and sell Testing Services in the United States of America; provided, however, that Research Tests and Testing Services shall only be performed pursuant to protocols and procedures reasonably acceptable to Myriad and approved by Myriad in writing prior to the performance of any such Research Tests and Testing Services. University may extend such rights to any Affiliate which is an educational or non-profit corporation upon written notice to Myriad and upon written agreement of such Affiliate to be bound by all terms and provisions hereof (a "Permitted Affiliate"). University shall have no right to grant sublicenses or to conduct any such Testing Services or Research Tests through any non-Affiliates without Myriad's consent.

2.2. The rights conveyed herein by Myriad are in all respects subject to the terms and conditions of this Agreement, including without limitation the warranties of University contained in Section 5 hereof.

2.3. Myriad and University agree to collaborate in the following activities:

a) University shall conduct such academic research activities as it shall determine involving BRCA1 and shall keep Myriad generally advised of the work of its research faculty in conducting such research. University may publish the results of such research, provided that no confidential or proprietary information of Myriad is disclosed. Myriad shall be provided with a copy of the manuscript of any such publication at least thirty (30) days prior to submission for publication.

b) Myriad may, from time to time and in its sole discretion allow University faculty members to send samples to Myriad's laboratory facilities for testing at reduced rates in order to support research activities involving BRCA1 or other disease predisposing genes.

2.4. University hereby grants Myriad (i) a right of first refusal to obtain an exclusive license to commercialize any invention resulting from activities of University pursuant to this Agreement under terms to be negotiated in good faith and (ii) a non-exclusive, royalty-free license under any invention resulting from activities of University pursuant to this Agreement relating to testing for the presence or absence of BRCA1 mutations.

2.5. University shall have the right to perform Research Tests provided that no fee is charged for such tests and provided that no direct clinical use shall be made of any Research Test results.

2.6. University shall have the right to perform Testing Services at University but only to the extent that such Testing Services are ordered by physicians affiliated with University or its Affiliates. As consideration for such rights University shall pay to Myriad an amount equal to (i) $30 for tests to detect a single mutation, and (ii) $45 per test for all other Testing Services actually performed. Additionally, University shall agree that, in exchange for the licenses granted hereunder, University and its Permitted Affiliates shall use Myriad to perform all other BRCA1 tests covered by patents owned or controlled by Myriad which are ordered by physicians through University or its Permitted Affiliates during the term of this Agreement.

2.7. University shall keep and require its Permitted Affiliates to keep complete and accurate records of all Testing Services and Research Tests performed. Myriad shall have the right at its expense to audit the performance of Research Tests and Testing Services and laboratory protocols, testing procedures, and quality control procedures at University, provided that confidentiality of patient records shall at all times be maintained by University. Myriad shall also have the right at its expense, through a certified public accountant or like person reasonably acceptable to University, to examine such records relating to Testing Services during regular business hours during the life of this Agreement and for six (6) months after its termination; provided, however, that such examination shall not take place more often than once a year, and shall not cover such records for more than the preceding three (3) years and provided further that such accountant shall report to Myriad only as to the accuracy of such sales and the payments required pursuant to this Agreement.

2.8. Within thirty (30) days after the close of each calendar quarter, University shall deliver to Myriad a true accounting of all Testing Services performed by University and its Permitted Affiliates during such quarter, and shall at the same time make all payments due to Myriad pursuant to this Agreement.

2.9. Late payments shall be subject to an interest charge of one and one-half percent (1 1/2%) per month.

3. Term of Agreement.

3.1. This Agreement shall commence upon the date first written above and continue for a period of three years unless sooner terminated by mutual consent of the parties, which consent shall not be unreasonably withheld. This Agreement may be renewed for additional periods of three years upon mutual agreement of the parties.

3.2. Notwithstanding the foregoing, the obligation to make payments pursuant to Section 2.6 of this Agreement shall expire upon the expiration, lapse or invalidation by a decision of a court or tribunal of competent jurisdiction from which no appeal is or can be taken, of the last remaining Patent in the United States of America which contains a valid and unexpired claim covering BRCA1, or its use, in the United States of America.

4. Confidentiality.

4.1. Myriad and University may each, in the course of collaborative activities under this Agreement, receive confidential and proprietary information from the other party. Each party agrees to maintain such information (which shall be marked or otherwise identified by the disclosing party as confidential) in confidence and will not use such information for any purpose except as authorized hereunder. Each party shall exercise, and shall cause its Affiliates, to exercise, a reasonable degree of care and at least the same degree of care as it uses to protect its own confidential information of similar nature to preserve the confidentiality of confidential information disclosed by the other party. Each party shall safeguard such information against disclosure to third parties, including without limitation employees and persons working or consulting for such party that do not have an established, current need to know such information for purposes authorized under this Agreement. This obligation of confidentiality does not apply to information and material that:

4.1.1. were properly in the possession of the receiving party, as shown by written records, without any restriction on use or disclosure, prior to receipt from the other party;

4.1.2. are at the time of disclosure hereunder in the public domain by public use, publication, or general knowledge;

4.1.3. become general or public knowledge through no fault of the receiving party or its Affiliates following disclosure hereunder;

4.1.4. are properly obtained by the receiving party from a third party not under a confidentiality obligation to the disclosing party hereto; or,

4.1.5. are required to be disclosed by order of any court or governmental authority; however, the receiving party shall provide the disclosing party with immediate notice of such required disclosure so that the disclosing party may have the opportunity to contest such disclosure.

4.2. Neither party shall make a public announcement or other publication regarding this Agreement (whether as to the existence or terms hereof) without the prior, written consent of the other, which consent shall not be unreasonably withheld; provided that the foregoing shall not prohibit any disclosure which, in the opinion of counsel to the disclosing party, is required by any applicable law or by any competent governmental authority.

5. Liability and Warranties

5.1. Myriad warrants that it has all power and authority to enter into this Agreement and to consummate the transactions contemplated hereby.

5.2. EXCEPT AS SET FORTH IN THIS PARAGRAPH 5, MYRIAD DISCLAIMS ANY AND ALL REPRESENTATIONS AND WARRANTIES, WHETHER EXPRESS OR IMPLIED, PERTAINING TO THE RESEARCH TESTS OR TESTING SERVICES OR THE PATENTS LISTED IN EXHIBIT A, INCLUDING BUT NOT LIMITED TO ANY IMPLIED WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE OR NON-INFRINGEMENT.

5.3. University warrants that it is an educational or non-profit corporation, duly organized under the laws of ______ and has full power and authority to enter into this Agreement and to consummate the transactions contemplated hereby.

5.4. University warrants that it has all necessary regulatory approvals at the state and federal level to perform Research Tests and Testing Services. University further warrants that it will at all times conform to the protocols and procedures as reviewed and approved by Myriad pursuant to Section 2.1 hereof.

6. Infringement

6.1. University shall promptly inform Myriad of any suspected infringement, infringement or misappropriation, by any third party, of Patents.

6.2. Myriad may bring suit with respect to Patents on its own and shall bear all costs of, and shall exercise all control over, any such suit. Myriad may, at its expense, cause Licensee to be joined in the suit as a plaintiff. Recoveries, if any, whether by judgment, award, decree or settlement, shall belong solely to Myriad. Any expenses incurred by University as a result of being added to such suit by Myriad shall be reimbursed by Myriad.

7. Indemnification.

7.1. Myriad shall not under any circumstances be liable to University or any third party for claims for any incidental, consequential, indirect or special damages, including any lost profits or savings, arising from any breach of warranty or the performance or breach of any other provision of this Agreement or the use or inability to use the Patents, or for any claims arising in tort, personal injury, product liability, or patent infringement.

7.2. University agrees to, at its expense, defend, indemnify and hold Myriad and its Affiliates harmless from and against any costs, expenses, or damages resulting from, or otherwise arising out of Research Tests or Testing Services performed by University, including, without limitation, the advertising or selling of Testing Services by University.

7.3. Indemnification provided Myriad under this Agreement shall extend also to Myriad's Affiliates, officers, directors, shareholders, successors, assigns, agents, employees, and insurers to the extent the same become subject to such claim in such capacity. Myriad shall provide University with written notice of any claim or action within ten (10) days of its receipt thereof and shall afford university the right to control the defense and settlement of such claim or action. Myriad shall provide reasonable assistance to the indemnifying party in the defense of such claim or action. If the defendants in any such action include both Myriad and University and any party concludes that there may be legal defenses available to it which are different from, additional to, or consistent with, those available to other(s), that party shall have the right to select separate counsel to participate in the defense of such action on its behalf and such party shall thereafter bear the cost and expense of such separate defense. No party shall settle any such claim or action in a way that prejudices or adversely impacts another party to this Agreement without the prior approval of such other party (which approval shall not be unreasonably withheld).

7.4. University shall maintain and will continue to maintain insurance coverage appropriate to the risks involved in marketing Testing Services and will annually present evidence to Myriad that such coverage is being maintained if so requested. University will furnish a copy of each such insurance policy obtained and agrees that such insurance shall be in a form and in an amount reasonably acceptable to Myriad.

8. Early Termination

8.1. In the event that either party materially breaches any of the terms, conditions, or agreements contained in this Agreement to be kept, observed or performed by it, then the other party may terminate this Agreement, at its option and without prejudice to any of its other legal or equitable rights or remedies, by giving the party who committed the breach sixty (60) days notice in writing, specifying the exact nature of the breach. During such sixty (60) day period, the notified party may cure such breach and, if cured, this Agreement shall continue uninterrupted.

8.2. This Agreement will automatically terminate if University files for protection under applicable bankruptcy laws, becomes insolvent, makes an assignment for the benefit of creditors, appoints or suffers appointment of a receiver or trustee over its property, files a petition under any bankruptcy or insolvency act or has such petition filed against it, or if University is terminated or dissolved for any reason.

8.3. Upon termination of this Agreement, Myriad shall have the right to retain any sums already paid by University, and University shall pay all sums accrued hereunder which are then due.

8.4. The provisions of Sections 2.4, 4, 5 and 7 hereof shall survive the termination or expiration of this Agreement.

9. Force Majeure

If the performance of any part of this Agreement by either party, or if the obligation of either party under this Agreement is prevented, restricted, interfered with or delayed by reason of any cause beyond the reasonable control of the party liable to perform, unless conclusive evidence to the contrary is provided, the party so effected shall use its reasonable best efforts to avoid or remove such causes of non-performance and shall continue performance with the utmost dispatch whenever such causes are removed. When such circumstances arise, the parties shall discuss what, if any, modification of the terms of this Agreement may be required in order to arrive at an equitable solution.

10. Assignment

This Agreement shall be binding upon and inure to the benefit of the successors in interest of the respective parties. Neither this Agreement, nor any interest hereunder, shall be assignable by University without the prior written consent of Myriad.

11. Notices

Any notices required or permitted under this Agreement shall be sent by certified mail, postage prepaid, recognized courier service, or confirmed (receipt acknowledged) facsimile to the following addresses of the party:

University: University of Pennsylvania Medical
Center 415 Curie Boulevard, Rm. 475
CRB
Philadelphia, PA 19104-6145
Attention: Haig H. Kazazian, Jr., M.D.,
F.A.C.M.G.

Myriad: Myriad Genetics, Inc.
320 Wakara Way
Salt Lake City, Utah 84108
Attention: Bill Hockett

12. Miscellaneous_Provisions

12.1. This Agreement constitutes the entire agreement between the parties and supersedes all written or oral agreements or understandings concerning the subject matter thereof or in conflict with their terms.

12.2. This Agreement shall be governed by, construed in accordance with, the laws of Utah without giving effect to its principles of Conflicts of Law.

12.3. Any dispute between the parties hereunder, other than a dispute relating to patent infringement, which cannot be resolved by good faith, negotiation between the parties over a period of at least ninety (90) days shall be resolved by arbitration conducted in the English language in Salt Lake City, Utah before a panel of three arbitrators under the then current rules and procedures of the American Arbitration Association, or other rules and procedures as the parties may agree. The prevailing party in such proceeding shall be entitled to an award of its reasonable attorneys' fees and other costs, including the fees and expenses of arbitrators, provided that the same may be apportioned between the parties by the arbitrators if they determine that each party has prevailed in part. The arbitral award shall be binding and conclusive on both parties and may be enforced in any court of competent jurisdiction. Notwithstanding the foregoing, either party may, on good cause shown, seek a temporary restraining order and/or a preliminary injunction from a court of competent jurisdiction, to be effective pending the institution of the arbitration process and the deliberation and award of the arbitration panel.

12.4. No waiver by a party of any breach of this Agreement, no matter how long continuing or how often repeated, shall be deemed a waiver of any subsequent breach thereof, nor shall any delay or omission on the part of a party to exercise any right, power or privilege hereunder be deemed a waiver of such right, power or privilege.

12.5. The relationship between the parties is that of independent contractor and contractee. University shall not be deemed to be an agent of Myriad in connection with the exercise of any rights hereunder, and shall not have any right or authority to assume or create any obligation or responsibility on behalf of Myriad. University shall not use the name of Myriad in any way in connection with the performance of Research Tests or Testing Services by University.

12.6. In the event any portion or provision of this Agreement shall be deemed unenforceable, as written or applied, the balance of such portion or provision and the balance of this Agreement shall continue in full force and effect, as if such unenforceable portion or provision had been deleted or rendered inapplicable to the situations to which such unenforceable portion or provision cannot legally be applied.

IN WITNESS WHEREOF, the parties have executed this Agreement, individually or by their duly authorized officers, as appropriate, on the date first written above.

Myriad Genetics, Inc.	University of Pennsylvania Medical Center
By: ________	By: ________
Title: ______	Title: ______

APPENDIX A

PATENTS

United States Patent Number 5,693,473 - "Linked Breast and Ovarian Cancer Susceptibility Gene", Dec. 2, 1997.

United States Patent Number 5,709,999 - "Linked Breast and Ovarian Cancer Susceptibility Gene", Jan. 20, 1998.

United States Patent Number 5,710,001 "17q-linked Breast and Ovarian Cancer Susceptibility Gene", Jan. 20, 1998.

United States Patent Number 5,747,282 - "17q-linked Breast and Ovarian Cancer Susceptibility Gene, May 5, 1998.

United States Patent Number 5,753,441 "17q-linked Breast and Ovarian Cancer Susceptibility Gene, May 19, 1998.

EXHIBIT 3

O'Melveny & Myers LLP

August 26, 1998

CONFIDENTIAL DRAFT

Haig H. Kazazian, Jr., M.D.
Director, Genetic Diagnostic Laboratory
University of Pennsylvania Medical Center
415 Curie Blvd., Room 475 CRB
Philadelphia, PA 19104-6145

Dear Dr. Kazazian,

I represent Myriad Genetics, Inc. As you know, Myriad is the owner of United States Patent Nos. 5,693,473; 5,709,999; 5,710,001; 5,747,282; and 5,753,441 covering, among other things, the BRCA1 gene sequence, mutations in the BRCA1 gene, probes used in testing for such mutations, and methods for detecting alterations in the BRCA1 sequence.

It has come to Myriad's attention that you are engaged in commercial testing activities that infringe Myriad's patents. I also understand that you are prepared to submit a license proposal for Myriad's consideration. Unless and until such a license arrangement is completed, however, you should cease all infringing testing activity. Myriad does not object to the completion of testing for samples currently in process, but further samples should not be tested. Myriad will assist you in testing any samples that you receive after the date of this letter.

This notification does not apply to research tests conducted under an IRB approved protocol to determine the presence or absence of BRCA1 mutations for the purpose of furthering non-commercial research programs, the results of which are not provided to the patient and for which no money is received from the patient or the patient's insurance.

Please confirm in writing that you have stopped the infringing testing activity. I look forward to your prompt response.

Very Truly Yours,

/s/ George A. Riley

George A. Riley
of O'MELVENY & MYERS LLP

cc: Dr. Alan Dickenson

EXHIBIT 4

Myriad

June 10, 1999

Robert R. Terrell
Office of General Counsel
University of Pennsylvania
221 College Hall
Philadelphia, PA 19104-6303

Dear Mr. Terrell,

It has come to our attention that Dr. Haig H. Kazazian, Jr. of the University of Pennsylvania is continuing to willfully engage in commercial BRCA1 and BRCA2 genetic testing activities, in violation of the University of Pennsylvania's previous assurances that such commercial testing activities would be discontinued. As you are aware, Myriad previously offered Dr. Kazazian a license to conduct commercial testing of BRCA1 and BRCA2 mutations on the same terms accepted by various other third parties, which offer was refused by Dr. Kazazian.

We believe that Dr. Kazazian's commercial testing activities infringe one or more of the following U.S. patents owned by Myriad Genetics: 5,693,473; 5,709,999; 5,710,001; 5,747,282; 5,753,441, and 5,837,492.

It has been Myriad Genetic's long-standing policy to permit and encourage BRCA1 and BRCA2 research performed in the principal investigator's own genetic testing laboratory, provided that such research is funded by a bona fide granting agency (such as the NCI or ACS). Genetic testing services which ate paid for by a third party, regardless of the source of that party's funds, are inherently commercial in nature.

Myriad Genetics regards Dr. Kazazian's genetic testing services which are paid for by third parties that are not bona fide granting agencies to be commercial in nature and demands that the University of Pennsylvania discontinue offering and conducting all such commercial genetic testing services.

We request again that you provide us with appropriate written assurances that the University of Pennsylvania has stopped providing the infringing tests. I would be happy to speak with you to discuss this matter, if you feel it would be helpful. I look forward to your prompt response.

Sincerely,

/s/ Christopher L. Wight

Christopher L. Wight
General Counsel

cc: Dr. Haig Kazazian
Alan Dickason

EXHIBIT 5

University of Pennsylvania
Office of the General Counsel
133 South 36th Street, Suite 300
Philadelphia, PA 19104-3246
Telephone: 215-746-5200
Facsimile: 215-746-5222
September 10, 1999

By FAX and by UPS Next Day Air

Christopher L. Wight, Esq.
Myriad Genetics, Inc.
320 Wakara Way
Salt Lake City, Utah 84108

Dear Mr. Wight:

Thank you for taking the time to speak with me on August 25th about Myriad's position concerning BRCA1 testing activities. This letter is to follow up on our conversation, and to reply to your letters of June 10 and August 31.

First, I would like to emphasize that neither Dr. Kazazian nor the University of Pennsylvania has violated any previous assurance made to Myriad. The letter of August 26, 1998 from Myriad's counsel, George Riley, to Dr. Kazazian demanded that Dr. Kazazian cease certain testing activity alleged to infringe Myriad's patents, but expressly stated that:

> This notification does not apply to research tests conducted under an IRB approved protocol to determine the presence or absence of BRCA1 mutations for the purpose of furthering non-

commercial research programs, the results of which are not provided to the patient and for which no money is received from the patient or the patient's insurance.

In a telephone conversation with me Mr. Riley repeated that Myriad's demand did not apply to research tests as defined in the letter, and I confirmed that understanding in my letter of December 8, 1998 to Mr. Riley. Since that time, the University has conducted its activities in good faith in accordance with that understanding. Prior to your most recent correspondence, Myriad had not restricted the scope of "research testing" to tests for which no money is received from any third party, or to research carried out only at the testing institution.

Myriad's current position that "providing genetic testing services to a third party and receiving payment for such services is inherently commercial in nature, whether or not such third party is using the genetic testing services in connection with research," is a substantial change from Myriad's prior position, and serves to restrict further the scope of "research testing" previously permitted by Myriad. Moreover, Myriad's current position is flatly inconsistent with Dr. Critchfield's September 15, 1998 representation to Dr. Susan G. Nayfield of NCI that Myriad supports NCI sponsored research "without reservation," and his assurance that Myriad "will not interfere with these research activities in any way, because to do so would undermine our own goal of understanding the clinical implications of inherited mutations in the BRCA1 and BRCA2 genes." By prohibiting researchers from providing research testing support to other publicly-funded researchers, Myriad clearly interferes with publicly-funded research, inhibits research collaborations, and makes itself the sole source for research testing for those researchers who are not able to conduct the tests themselves.

Notwithstanding our concern over Myriad's change in position, we are willing to explore possible licensing arrangements, provided that any such arrangement permits Dr. Kazazian's laboratory to engage in a reasonable range of testing activities and does not restrict the researchers' ability to exercise independent scientific judgment in the selection and analysis of tests.

In light of Myriad's most recent demand and while we explore the possibility of a licensing arrangement, the University agrees that it will not accept samples for BRCA1 research testing from third parties where no University of Pennsylvania researcher is the principal investigator or co-investigator named on the grant funding the research. In order to avoid any future misunderstanding concerning Myriad's position, please confirm that Myriad does not object to genetic testing activities conducted at the University of Pennsylvania by or for a University of Pennsylvania researcher who is a named investigator on a grant from a bona fide granting agency that supports the research.

Sincerely.

Robert R. Terrell

Cc: Haig H. Kazazian, Jr.
Arupa Ganguly
Barbara Weber
Susan G. Nayfield, M.D.

EXHIBIT 6

Myriad

BY FEDERAL EXPRESS

September 22, 1999
Robert R. Terrell
University of Pennsylvania
Office of the General Counsel
221 College Hall
Philadelphia, PA 19104-6303

Dear Mr. Terrell,

I acknowledge receipt of your letter of September 10, 1999, and appreciate your willingness to discuss and resolve this matter with Myriad.

I would like to respond to and clarify several points raised in your letter. First, Myriad's objection to Dr. Kazazian engaging in commercial testing activities has not changed at any time. Myriad has consistently allowed research institutions to conduct genetic tests in support of legitimate research activities, provided such tests have no commercial objective. As you noted in your letter to me, Myriad's position toward non-commercial research allows

> ... research tests conducted under an IRB approved protocol to determine the presence or absence of BRCA1 mutations for the purpose of furthering non-commercial research programs, the results of which are not provided to the patient and for which no money is

received from the patient or the patient's insurance.

These guidelines were created both to assure that patients receive only the most accurate genetic test results possible and to protect the significant investment made by Myriad in developing its genetic testing business.

I appreciate your personal reassurances that Dr. Kazazian has not violated these guidelines; however, it is our understanding that Dr. Kazazian did not in fact comply with these guidelines in that (1) his test results were provided to patients for the primary purpose of clinical management, and (2) he did not obtain approval from the University of Pennsylvania's IRB to perform the research, which was actually performed at another institution. Moreover, Dr. Kazazian was performing the tests on behalf of a third party customer and charging the customer a fee to conduct the test. As a result of Dr. Kazazian's activities, Myriad lost customers who chose instead to order their tests from Dr. Kazazian's laboratory. Viewed as a whole, it was evident that Dr. Kazazian was simply engaging in commercial contract research for which he charged a fee.

It was clearly not Myriad's intent that the above guideline constitute a license to perform contract research testing, which is blatantly commercial in nature. Since Dr. Kazazian did not comply with the terms of Myriad's guidelines, Myriad felt it necessary to reiterate and clarify its position that genetic testing done with the object of receiving economic gain is inherently commercial and is therefore an unauthorized infringement of Myriad's patent rights. Myriad's most recent statement - that providing genetic testing services to a third party and receiving payment for such services is inherently commercial in nature was simply intended to further clarify its policy against commercially infringing activities.

With respect to forward-looking activities of the University of Pennsylvania, your agreement that you will not accept samples for BRCA1 research testing from third parties where no University of Pennsylvania researcher is the principal investigator *or co-investigator* named on the grant funding the research is, unfortunately, not acceptable, since multiple individuals may be named as co-investigators, even if they are not affiliated with the institution that is the recipient of the grant money. This would permit Dr. Kazazian to continue the same commercial genetic testing activities for a fee to which Myriad objects. Myriad reiterates its position that it is willing to permit Dr. Kazazian to engage in bona fide genetic testing research activities, provided he obtains a University of Pennsylvania IRB approval for research at the University, results are not returned to patients, and the University of Pennsylvania or one of its employees is the direct recipient of the grant supporting such research activities. We request that you provide Myriad with written assurances that the University of Pennsylvania is no longer accepting samples from third parties, except as permitted above.

On another matter, Myriad was recently informed by one of its customers that a University of Pennsylvania employee, Dr. Debra Leonard, made false and disparaging remarks about Myriad's commercial genetic tests. Specifically, our customer was alarmed that Dr. Leonard stated that Myriad's test results were of poor quality and not accurate, and further stated that Myriad encouraged patients to obtain genetic tests without appropriate counseling from health care providers or genetic counselors. Both of these statements are blatantly false. Myriad has taken extraordinary steps to assure that its genetic tests are the most accurate and reliable tests available anywhere in the world. Myriad also educates health care providers and genetic counselors to correctly identify those patients who should receive its genetic tests (including screening out those patients who should *not* receive it), and provides health care providers with a list of genetic counselors to encourage patients to seek informed advise from professionals. Moreover, it is ironic that Dr. Kazazian's laboratory at the University of Pennsylvania has in fact on multiple occasions produced the very type of inaccurate genetic test results of which Dr. Leonard has falsely accused Myriad of producing. To add to the irony, these inaccurate results produced by Dr. Kazazian's laboratory were detected by Myriad at the request of the patient. It is unfortunate that a University of Pennsylvania's representative, speaking on the topic of "ethics," would resort to making false and disparaging comments concerning Myriad's commercial activities.

As you will appreciate, such disparaging comments do little to engender goodwill between our institutions, and make it very difficult for me to advocate accommodating Dr. Kazazian's requests for a license from Myriad. We would sincerely appreciate your efforts in curbing this growing pattern of disparagement of Myriad Genetics by explaining to your employees that false disparagement of the commercial products and services of another is not only unethical, but also actionable under the law.

Thank you again for your cooperation. I look forward to receiving your written assurances that the University of Pennsylvania will discontinue offering commercial genetic testing services to third parties.

Sincerely,

/s/ Christopher L. Wight

Christopher L. Wight, General Counsel

EXHIBIT 7

Myriad

September 15, 1998

Susan G. Nayfield, MD
National Cancer Institute
6120-6130 Executive Boulevard
Rockville, MD

Dear Dr. Nayfield,

I would like clarify concerns that have arisen about how Myriad Genetics' *BRCA1* patent position might impact on research efforts sponsored by the National Cancer Institute. Let me unequivocally state that Myriad recognizes and strongly supports the need for research in the genetics of cancer. In particular, we believe that the research sponsored by the NCI contributes substantially to health of all patients, and we support such research without reservation. We will not interfere with these research activities in any way, because to do so would undermine our own goal of understanding the clinical implications of inherited mutations in the *BRCA1* and *BRCA2* genes.

Over the past several months we have contacted several laboratories engaged in *commercial testing* of the *BRCA1* gene. It is my understanding that you and others have seen a copy of a draft agreement sent to such facilities, entitled "Collaboration Agreement." This document was designed for the sole purpose of defining the conditions under which diagnostic laboratories may be allowed to conduct *commercial testing* for hereditary breast cancer. Any laboratory engaged solely in research analysis of *BRCA1* that received this document (and an accompanying cover letter) did so in error. Because our policy as defined by this document is intended specifically to license laboratories engaged in commercial testing, we assume that this policy is not of direct interest to the NCI whose interest is research.

We would like the NCI to be aware that we do offer testing services for grant-supported research by performing sequence analysis of *BRCA1* and *BRCA2* at a substantial discount, to facilitate research activities that will advance clinical knowledge in the area of cancer genetics. We are pleased to provide sequence analysis of *BRCA1* and *BRCA2* for several NCI-funded projects at present. For these research projects, we have no requirement to receive patient identifiers or accompanying clinical information, and we welcome samples that are coded to protect patient confidentiality. We specifically waive editorial privileges for such manuscripts, and we are happy to provide written assurance of this in advance.

We recognize that NCI-sponsored investigators may choose to analyze *BRCA1* and *BRCA2* in research laboratories, and we will not interfere with any such activities. We believe, however, that for protocols where results are provided to patients, Myriad Genetic Laboratories offers a substantial benefit over most research laboratories: as a CLIA-certified clinical laboratory we employ extraordinary safeguards designed to ensure test accuracy and patient confidentiality.

We welcome any comments you may have about our policies and programs, and hope to have the opportunity to support NCI-sponsored research activities in the future. Please feel free to contact me at 1-801-584-3501 should you have any questions.

Yours truly,

/s/ Gregory C. Critchfield

Gregory C. Critchfield, M.D., M.S.
President, Myriad Genetic Laboratories, Inc.

[Declaration of Elizabeth Swisher, filed August 26, 2009] [Caption Omitted In Printing] [Exhibit 1 Omitted]

I, Elizabeth Swisher, M.D., declare under penalty of perjury:

1. I am an Associate Professor of Obstetrics and Gynecology at the University of Washington School of Medicine, as well as the Medical Director of the Breast and Ovarian Cancer Prevention Program of the Seattle Cancer Care Alliance. My research and clinical specialty is focused on the genetics and treatment of gynecologic cancers, which include ovarian, cervical, uterine, vaginal, and vulvar cancers.

2. My laboratory is studying how ovarian cancer starts in order to determine better methods for prevention and early detection of ovarian cancer. I also study mechanisms of chemoresistance in ovarian cancers, and how the BRCA1 and BRCA2 genes influence response to chemotherapy.

3. My research interests have led me to become a member of the Steering Committee for the Breast Cancer Information Core (BIC). The BIC gathers information on BRCA genetic mutations, which are correlated with ovarian and breast cancer, to further the scientific community's ability to research the genetics of these cancers.

4. I am aware that Myriad Genetics controls patents on the BRCA1 and BRCA2 gene sequences. In this declaration, based on my professional knowledge and expertise, I describe two of my concerns with these patents: 1) the excessive control these patents give to the patentholder over genetic

information, including information about genetic variants, that impedes scientific inquiry, research, and clinical practice; and 2) the barriers presented by the patents to physicians in the U.S. who want to offer patients the international standard of care with respect to BRCA genetic testing.

Background

5. I completed my undergraduate studies at Yale University and earned my medical degree from the University of California, San Diego, in 1992. Following completion of my residency in obstetrics and gynecology at the University of Washington in 1996, I did a postgraduate fellowship in gynecologic oncology at Washington University. During my fellowship, I published several papers on the role of genetic mutations in endometrial cancers. I was then awarded a Research Training Scholar Award from the Women's Reproductive Health Research Career Development Program at the University of Washington.

6. I am currently an Associate Professor of Obstetrics and Gynecology at the University of Washington School of Medicine and an Adjunct Associate Professor in the Department of Medicine's Division of Medical Genetics at the University of Washington. I also am the Medical Director of the Breast and Ovarian Cancer Prevention Program of Seattle Cancer Care Alliance, an Affiliate Investigator for the Division of Public Health Sciences for the Fred Hutchinson Research Center, and a member of the University of Washington's Advisory Board on Women's Reproductive Health Research.

7. I am a physician, surgeon, and researcher. I treat women who have been diagnosed with gynecologic cancers, advise women regarding monitoring, prevention, and hereditary susceptibility, and research potential treatments for BRCA-positive ovarian cancers. Much of my work has investigated the links between BRCA genetic mutations, hereditary risk for ovarian cancer, and chemotherapy. My recent publications are listed in detail in my attached curriculum vitae and include, "Secondary BRCA1 mutations in BRCA1-mutated ovarian carcinomas with platinum research," "Management of Women with Inherited BRCA1 and BRCA2 Mutations," and "Genomic structure of chromosome 17 deletions in BRCA1 associated ovarian cancers"

8. I have taught numerous undergraduate and graduate classes, engaged in extensive resident and fellow teaching, and offered continuing medical education courses. Examples of my classes include "Ovarian Cancer Risk Management," "BRCA-Positive Ovarian Cancer: Can Cisplatin Resistance be Predicted and Can PARP be Therapeutically Targeted?," "Oncogenes/Tumor Suppressor Genes," and "Recognition and Testing for Hereditary Cancer Risk."

9. I am a leader and member of numerous professional organizations, as noted fully in my curriculum vitae. I serve on the Steering Committee for the Breast Cancer Information Core (BIC) and on the Cancer Genetics Education Committee of the American Society of Clinical Oncology. I am also a member of the American Association of Cancer Research, the American

College of Obstetricians and Gynecologists, and the Society of Gynecologic Oncologists.

BRCA1/2 Genes and Ovarian Cancer

10. Ovarian cancer is the eighth most common cancer in women and causes more deaths in the Western world than any other gynecologic cancer.

11. Between 10 and 15% of ovarian cancers are inherited genetically. For women who are diagnosed under the age of 50 years old, approximately 80% of inherited ovarian cancers are caused by BRCA1 mutations, and approximately 20% are caused by BRCA2 mutations. Women with inherited BRCA1 mutations have a 40-52% cumulative risk of ovarian cancer by the time they reach 70 years old. For women with inherited BRCA2 mutations, the risk is approximately 15- 25%.

12. The existence of BRCA1/2 mutations is an important factor in clinical care. If a patient is positive for a mutation, doctors frequently recommend ovarian cancer risk-reducing strategies that might include increased surveillance, chemoprevention through oral contraceptives, and/or oophorectomy (ovarian surgery). Bilateral salpingo-oophorectomy (removal of both ovaries and the fallopian tubes) is associated with an 80-90% reduction in ovarian and fallopian tube cancer and a 50-60% reduction in breast cancer.

13. The BRCA1 and BRCA2 genes are not only cancer susceptibility genes, but also are critical determinants of clinical sensitivity to chemotherapy. Some of my recent work has focused on the use of platinum compounds to treat BRCA1/2-mutated

carcinomas. Patients with BRCA1/2-mutated ovarian cancer consistently have a better prognosis compared with noncarriers if they receive platinum-based chemotherapy. Thus, BRCA1/2 genetic status can be a vital factor in deciding course of treatment.

Breast Cancer Information Core (BIC)

14. The scientific community has long recognized the importance of sharing data about genetic mutations in centralized, public databases. While publication of genetic information in medical and scientific journals increases scientific knowledge, a more efficient way of providing researchers with broad access to mutation data is through centralized databases. These databases can aggregate reports of findings of various genetic variants, and thus can have substantial value to the scientific community.

15. A steering committee of the National Human Genome Research Institute (NHGRI), a part of the National Institutes of Health, engaged in an international effort to develop a clearinghouse for information on the BRCA1 and BRCA2 genes. In 1995, the BIC was formed as a result of this worldwide effort. The BIC is an open access, on-line database that is a central repository for information regarding mutations and polymorphisms in the BRCA genes. It helps facilitate identification of deleterious mutations (mutations associated with a higher risk of cancer) and provides a mechanism to collect and distribute data about genetic variants. The BIC also provides technical support in the form of detection protocols, primer sequences, and reagent access. Beginning in 2005, the BIC began to post expert evaluations of some of the BRCA1 and BRCA2 variants recorded in its database.

16. The BIC is run by staff members who work on a volunteer basis. Since 2004, I have served on the BIC Steering Committee, which consists of ten to twelve investigators who work in the field of cancer genetics. We meet monthly via teleconference to discuss issues of relevance to the database.

17. The BIC's data are derived from both published literature and direct online entries made by contributors all over the world. Laboratories submit data, and once reviewed by members of the steering committee to ensure that they meet certain quality standards, the data are added to the database. The value of the BIC comes from the amount and quality of data provided by the scientific community.

18. The BIC is used by researchers in a number of ways. A researcher anywhere in the world can access the BIC and look up information on a particular variant. A researcher can incorporate data regarding mutations and variants reported to BIC into studies he or she is conducting. Many of the studies that have been performed that involve BRCA-affected individuals draw on BIC data. In recent years, there has been special attention paid to determining the meaning of variants of uncertain significance, which are variants on the BRCA genes whose connection to cancer is unknown. Variants of uncertain significance pose a difficult clinical problem, as we cannot easily advise patients who have such variants about health decisions. By gathering information about variants of uncertain significance in one place, the BIC plays an important role in helping to elucidate these variants.

19. For several years, Myriad Genetics, like other laboratories around the world, submitted mutation and variant data to the BIC. Because Myriad controls clinical testing of the BRCA genes in the United States, and because more testing occurs in the U.S. than any other country, Myriad was the largest contributor of data to the BIC. It provided a majority of the reports regarding variants. However, Myriad stopped contributing its data approximately two years ago. As far as I know, it did not give any reason for its decision to the Steering Committee. For that reason, the U.S. essentially does not provide any data regarding BRCA variants identified in Americans.

20. The patents granted on the genes allow one entity in the U.S. to exercise enormous control over BRCA1 and BRCA2 mutation data. While Myriad has shared its data in the past, it now does not do so, to the detriment of the scientific community, patients, and public health. Once Myriad stopped contributing data, the BIC became a much less useful tool, both to researchers in the U.S. and globally. It is true that researchers do not have a formal obligation to contribute variant data to the BIC. However, each laboratory has an incentive to do so in order to benefit from the data contributed by others and to further scientific progress. This incentive evaporates when one laboratory controls most of the data about a gene.

21. Scientific researchers need access to more information about the BRCA1/2 genes, not less. Genes are so fundamental to medicine and science that any restriction that prevents researchers from analyzing genes or examining the effects of genes is

contrary to our efforts to promote scientific knowledge and improve medical practice.

Standard of BRCA1/2 Genetic Testing Provided to Patients in the United States

22. The BRCA1 and BRCA2 genes are large genes. 5,400 base pairs make up the nucleotide sequence that codes for the BRCA1 protein, and 10,200 base pairs make up the nucleotide sequence that codes for the BRCA2 protein. Mutations or variants can occur at any position along these sequences, taking the form of a substituted base, a small deletion or addition of one or more bases, or deletions and duplications of large sections of the gene.

23. Full sequencing is often the method used to identify when a base has been substituted at a single point in the sequence or where insertions or deletions of a small number of bases have occurred, because this method determines the order of bases in a sequence. However, full sequencing can miss large genomic rearrangements, where whole sections of the gene have been deleted or moved to a different part of the sequence.

24. A number of tests have been developed by researchers to better detect large rearrangements. The test that is now frequently relied upon is the multiplex ligation-dependent probe amplification (MLPA). MLPA was developed in Holland and can be applied to amplify any targeted gene sequence. MLPA is a high-resolution, simple, and relatively low cost test. It is used widely around the world and has been validated through numerous studies. MLPA kits for analyzing the BRCA1 and BRCA2 genes have

been developed and are offered commercially. The difference between using full sequencing and a test like MLPA to analyze a gene is analogous to the difference between proofreading a page for single letter typos and for misplaced paragraphs.

25. In 2006, I co-authored a study examining the frequency and types of undetected cancer-predisposing mutations in BRCA1 and BRCA2 that was published in the Journal of the American Medical Association (JAMA).[1] The study focused on cancer patients with severe family histories of breast or ovarian cancer who had tested negative for BRCA mutations under Myriad's commercial full sequencing test. We used MLPA as one alternative mode of analysis.

26. The study concluded that genetic testing, as carried out in the United States by Myriad, did not provide all available information to women at risk. The data indicated that "12% of those from high-risk families with breast cancer and with negative (wild-type) commercial genetic test results for BRCA1 and BRCA2 nonetheless carry cancer-predisposing genomic deletions or duplications in one of these genes."

27. We recommended MLPA followed by confirmation of the points along the sequence where the genomic sections of the sequence had been moved as the best mode of analysis for identifying BRCA1/2 large rearrangements in patients who had tested

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[1] Tom Walsh et al., *Spectrum of Mutations in BRCAI, BRCA2, CHEK2, and TP53 in Families at High Risk of Breast Cancer*, 295 JAMA (12) 1379-1388 (2006).

negative for BRCA1/2 by conventional sequencing. Our study reinforced a number of other studies that previously had come to the same conclusion: full sequencing, while an important analytical method, misses significant BRCA1/2 large rearrangements.[2] As such, all women with significant family history who receive negative test results should undergo testing for large rearrangements.

28. Our recommendation cannot be carried out by any clinical laboratory that might wish to do so. Because of the U.S. patents on the BRCA1/2 gene sequences, Myriad Genetics has the exclusive right to offer genetic testing to patients. Myriad has granted some limited licenses to a few laboratories and allows researchers to conduct genetic testing. However, to the best of my knowledge, Myriad has not allowed any other laboratory in the country to perform clinical full sequencing of the BRCA1 and BRCA2 genes or to offer large rearrangement testing.

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[2] Some of these studies include: S. Agata et al., *Large genomic deletions inactivate the BRCA2 gene in breast cancer families*, J. Med. Genet. 2005;42;e64; C. Hartmann et al., *Large BRCA1 Gene Deletions Are Found in 3% of German High-risk Breast Cancer Families*, Human Mutation 2004;24:534; M. Montagna et al., *Genomic rearrangements account for more than one-third of the BRCA1 mutations in northern Italian breast/ovarian cancer families*, Human Molecular Genetics 2003;12:1055-1061; I. Tournier et al., *Significant contribution of germline BRCA2 rearrangements in male breast cancer families*, Cancer Research 2004;64:8143-8147; S. Gad et al., *Bar code screening on combed DNA for large rearrangements of the BRCA1 and BRCA2 genes in French breast cancer families*, J. Med. Genet. 2002;39:817-821.

29. In response to the numerous studies published over the years documenting the inadequacy of full sequencing, Myriad began to offer a new test. Myriad's standard test, Comprehensive BRACAnalysis, consists of full sequencing of the BRCA1/2 genes and detection of five specific large rearrangements on the BRCA1 gene. In late 2006, Myriad began to offer the BRACAnalysis Rearrangement Test (BART), which looks for additional large rearrangements in the coding sequences of both BRCA1 and BRCA2.

30. The BART test is not available to many women who should have access to it. Myriad has strict criteria — that Myriad determines — for which patients should receive concurrent BART testing. BART will be run concurrently, at no additional cost, for patients who have personally experienced breast cancer before the age of 50 years, ovarian cancer at any age, or male breast cancer at any age, but only if the patient has at least two relatives on the same side of the family who were diagnosed with breast cancer before age 50 or ovarian cancer at any age.[3] Patients who do not meet these criteria must pay an additional $650 to order BART. Many insurance policies will not cover BART including Medicare. Approximately one-third to one-half of my patients for whom I request genetic testing do not meet Myriad's criteria; yet, I think most should receive this additional testing.

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[3] Myriad's criteria for including BART concurrently with BRACAnalysis are available at http://www.myriadresourceguide.com/pdfs/Myriad-Resource-Guide-BART-Criteria.pdf.

31. One recent study examined Myriad's criteria for automatic BART testing.[4] Myriad provides automatic BART testing for people with an estimated risk of having a BRCA1/2 mutation of more than approximately 30%.[5] The study authors concluded that these criteria are too strict, and that large genomic rearrangement screening should be offered to all non-Ashkenazi Jewish women whose estimated risk of having a BRCA1/2 mutation is greater than 10%, based on medical history, family history, and other factors. Their suggested criteria for offering BART testing are similar to previous criteria used to determine who should get gene sequencing. Therefore, if an individual has a personal and family history that suggests she would be offered genetic testing for BRCA1 and BRCA2, she probably should be offered both sequencing and testing for gene rearrangements.

32. Because it is a test performed exclusively by Myriad, not much is known in the scientific community about BART. It is my understanding that the sensitivity and specificity of BART has never been fully and independently validated.

33. In other parts of the world, where the BRCA1/2 gene patents appear not to be enforced or have been limited, the standard of care includes

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[4] M.D. Palma et al., *The Relative Contribution of Point Mutations and Genomic Rearrangements in BRCA1 and BRCA2 in High-Risk Breast Cancer Families*, Cancer Research 2008;68:7006-7014. The study found rearrangements using MLPA, a subset of which were confirmed by an alternate test, and also sent to Myriad for confirmation by BART.

[5] *Id.* at 7012.

large rearrangement testing using MLPA. To the best of my knowledge, MLPA on the BRCA1/2 genes is widely performed in Canada, Australia, and Europe. Myriad Genetics has published no formal comparison of BART with MLPA.

34. As a physician in the United States, I find myself unable to offer the international standard of care for my patients. Because I specialize in ovarian cancer, many of my patients are appropriate candidates for BRCA genetic testing. If they choose to go forward with testing, I must order the test through Myriad. However, the vast majority of them will not qualify for BART under Myriad's criteria even though my professional opinion is that large rearrangement testing should be done. For those who do not have the financial resources to pay for BART separately, neither I nor they can access that piece of information about their genes to help make medical decisions. For those who might be able to come up with the funds to pay for BART, I still cannot be confident that I am acting on the highest quality information because BART has not been fully and independently validated or compared to MLPA. I fear that I am ordering a second-rate test for my patients. More generally, I am concerned on behalf of my patients that the current system creates no incentive to create better and cheaper BRCA1/2 testing methods.

35. Today, I cannot offer my patients what I believe to be the best care related to BRCA1/2 genetic testing: a validated test that combines both full sequencing and large rearrangement analysis for all patients who are appropriate candidates for genetic testing. As a result of the BRCA1/2 gene patents and

the restrictions placed on genetic testing, this standard of care cannot be extended to patients in the United States. If the patents were invalidated, I have strong reason to believe that additional laboratories would offer large rearrangement BRCA1/2 testing, and I would order such testing for my patients.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Elizabeth Swisher

Elizabeth Swisher, M.D.

Executed on August 19, 2009

[Declaration of David Ledbetter, filed August 26, 2009] [Caption Omitted In Printing] [Exhibit 1 Omitted]

I, David H. Ledbetter declare under penalty of perjury:

1. I am Director of the Division of Medical Genetics and am the Robert W. Woodruff Professor of Human Genetics at Emory University School of Medicine. The Chair of our Department at Emory is plaintiff Stephen Warren.

2. My training and expertise are in the field of genetic testing. I received a PhD in Behavioral Genetics from the University of Texas at Austin in 1981.

3. Following completion of my PhD, I joined the faculty at Baylor College of Medicine in Houston as Assistant Professor and Director of the Kleberg Cytogenetics Laboratory, rising to the rank of full Professor in 1990. From 19993-1996, I served in the Senior Executive Service (SES6) of the federal government as Branch Chief of the Diagnostic Development Branch at the National Center for Human Genome Research (now the National Human Genome Research Institute). From 1996-2003, I served as the founding Chair of the Department of Human Genetics at the University of Chicago and held the Marjorie I. and Bernard A. Mitchell Professor of Human Genetics. Since 1992, I have served on the faculty of the Short Course in Medical and Experimental Mammalian Genetics in Bar Harbor, Maine.

4. I am a diplomat of the American Board of Medical Genetics (Clinical Cytogenetics) and a

Founding Fellow of the American College of Medical Genetics (ACMG), an organizational plaintiff in this case. I have served on the Board of Directors of the American Society of Human Genetics and the American College of Medical Genetics. While on the Board of Directors for the American College of Medical Genetics, a position statement against the patenting of human genes was developed and approved by the Board and remains in effect today.

5. In 1995, I was awarded the 12th Carter Lecturer and Medal Recipient from the British Clinical Genetics Society.

6. A full copy of my current curriculum vitae is attached as an Exhibit.

7. My research has focused on the molecular characterization of human developmental disorders. As a graduate student, I discovered the chromosome 15 deletion that causes Prader-Willi syndrome (obesity and mental retardation). Shortly thereafter, I described the deletion of chromosome 17 that causes Miller-Dieker lissencephaly ("smooth brain"), a neuronal migration disorder causing profound mental retardation. My lab developed improved techniques for diagnosing these and other microdeletion syndromes (fluorescence in situ hybridization or FISH diagnostic tests, which were more accurate than high-resolution chromosome banding techniques that were used previously).

8. As Director of the Division of Medical Genetics, I am responsible for very large genetic testing laboratories at Emory University School of Medicine. These laboratories provide clinical testing services to a large number of patients and families

with genetics diseases (over 28,000 tests performed per year) and include biochemical genetics, cytogenetics and molecular genetics testing.

9. Our genetic testing laboratory is a state-of-the-art clinical laboratory that offers full gene sequencing and testing for structural mutations. Test results are initially analyzed by experienced technologists and, where deleterious mutations are identified, these are interpreted, or correlated with disease risk. Our lab directors review the detailed results of all of our genetic tests and determine the final interpretation which is entered into a report.

10. Our genetic testing laboratory has the all of the personnel, expertise, equipment and facilities necessary to do comprehensive mutation analysis (including full gene sequencing and high-resolution deletion/duplication analysis) of any human gene, including sequencing of the BRCA1 and BRCA2 genes.

11. As an academically based genetics testing laboratory, a central part of our mission is to develop and implement new, better genetic tests that are more powerful, sensitive and accessible to patients. All of my research and most of the research of the faculty in my Division is "translational research" — research that aims to move new gene discoveries and technologies into clinical practice. In the last 3 years our molecular genetics laboratory has developed new gene sequencing tests for over 200 rare genetic diseases, many of which were previously unavailable as clinical tests. This work has depended upon our close collaboration with basic scientists at Emory and elsewhere.

12. Our program has developed several other techniques that are helping to revolutionize cytogenetics in research in clinical diagnostic laboratories. We are leaders in the development of microarray and high-throughput sequencing for clinical genetics testing.

13. For the past twenty-five years of my professional career, I have been aware of the detrimental impacts of gene patents, exclusive licensing, and genetic testing monopolies on clinical care. While at Baylor College of Medicine, I worked to discourage colleagues in my department from participating in an exclusive licensing practice. I was working at NIH with Dr. Francis Collins during the "race" to identify the BRCA genes by multiple groups, primarily funded by U.S. federal funds (National Institutes of Health). I was quite aware of the "winning team" being a collaboration of investigators at the University of Utah, Myriad and U.S. government labs and the subsequent patenting of and exclusive licensing of the BRCA 1 and BRCA2 genes that followed.

14. When I moved into doing translational research at the University of Chicago in 1996, the impact that the patenting and exclusive licensing of genes can have on research were made especially clear to me. Here, our quest to find new genes and undergo disease research was heavily directed by the patent landscape. We felt forced to design our research and business model so as to avoid genes that had been patented and exclusively licensed, since it had been made clear to us that we would not be able to obtain licenses to offer testing in those areas. Similarly, any enthusiasm we had for working

on a particular disease was at risk of being deflated by announcements that a gene associated with that disease had been patented and exclusively licensed. For us, this meant that we could not participate in developing and improving tests associated with those diseases and that we could not work to make such tests accessible to our patients.

15. At Emory, we have also had to design our research and business plan around gene patents. Because of the interdependence of our translational research with our clinical testing activities, we are only able to invest in research for those diseases in which we will be free to offer genetic testing when we are successful in developing a new or improved clinical test. When a gene patent and exclusive licensing situation creates a genetic testing monopoly, we are forced to avoid performing research for this particular disease and therefore cannot contribute our cutting-edge technologies to the improvement of clinical testing for this patient population. This strong disincentive to perform translational research applies to many other academically based genetics testing laboratories, thus depriving patient populations from the active research involvement of some of the best scientists and institutions in the world.

16. Our lab explicitly avoided the BRCA1 and BRCA2 genes even though we could have developed a better test than Myriad was offering. For example, we have understood for some time that simply sequencing the coding regions of the two genes does not find all known causative mutations that have been associated with an increased risk of developing breast and/or ovarian cancer. Sequencing will only

uncover approximately 70% of the causative mutations. A significant portion of the remaining 30% of known mutations are structural mutations — primarily large rearrangements — in the gene that disrupt its function. Testing for these requires applying alternative methods. The existence of these structural mutations and the methods for looking for them were known for a long time before Myriad started to test for them. Instead, Myriad employed a partial testing strategy. That means that a significant number of women were receiving false negative testing results. Still today, Myriad does not reflexively test for these additional structural mutations in the event of a negative sequencing test result.

17. By contrast, our lab offers comprehensive genetic analyses. In the event that we do not find known genetic alterations through gene sequencing, we automatically offer to look for structural mutations using cutting-edge microarray technologies to detect copy number. We offer this for all of our genetic testing. Our lab's leadership in microarray analysis means that we can conduct this additional testing more efficiently than most other labs.

18. If the BRCA 1 and BRCA2 patents were invalidated, our lab would immediately begin offering comprehensive BRCA1 and BRCA2 testing. I estimate that we could have a BRCA testing program up and running within one month's time. We have all of the personnel and expertise that we need to offer comprehensive BRCA testing. Our leadership in developing high-throughput sequencing assays means that we have access to some of the most

advanced equipment and techniques that would allow us to offer a highly efficient testing program. As we do for other whole gene tests, we would offer full sequencing, and for each case where standard sequencing does not reveal a pathogenic mutation, we would recommend and offer testing for structural mutations, utilizing our state-of-the art microarray technology. We would sequence and analyze the BRCA1 and BRCA2 genes for the named plaintiffs.

19. Our lab is of the view that clinical testing data should be contributed to a public, open database on a quick turnaround basis. The sharing of data benefits the entire clinical community whereas private, proprietary database inhibit the development of knowledge. If we were to offer BRCA testing, we would contribute all of our research and clinical data as we do in the case of all of our genetic testing.

20. One of the reasons data sharing is so essential in molecular diagnostics is that often we see genetic alterations that are difficult to interpret. These are referred to as "variants of unknown significance." Developing an understanding of which of these variants are pathogenic and which are benign requires large datasets. These can best be obtained by pooling data from many labs. When one party hoards all of the clinical data for a particular gene, it prevents the greater genetic community from being able to analyze this data and come to conclusions about the significance of these variants. If Myriad had been sharing its data and permitting other labs to analyze the genes, it is quite possible that researchers or clinicians in other labs would have been able to understand the significance of some variants that Myriad now labels "unknown

significance." That is why we routinely share such data. It is also why the participants of the Human Genome Project shared their sequence data, without restriction.

21. Our method for looking at structural mutations is different from the method that Myriad currently employs. Where multiple labs offer multiple methods of testing, it becomes possible to compare these different methods, and this ultimately may lead to improved testing quality.

22. After we sequence a gene we look at it to see if it has variants. That is, we compare it to the normal or wild-type gene to see if there are any differences. If there are differences, we try to determine if any of those differences have clinical significance. This process, of looking at a gene to see if there are variants and analyzing it to determine the clinical significance of those variants is routine and done by literally hundreds of labs all over the world every day. Indeed, analyzing the results of a sample taken from a patient to determine if it varies from the norm and if that variance has significance is the entire point of clinical laboratory work and is done not only with genes but in a huge variety of contexts.

23. By vigorously enforcing its patents and maintaining a monopoly on clinical diagnostic testing, Myriad is depriving women of an opportunity for a second opinion. Women who receive a negative result cannot know for certain what the rate of false negatives might be. Women who receive a positive result cannot confirm the lab's findings or seek a second opinion on the interpretation of those results. In addition to second opinions, proficiency testing and sample exchange programs are other aspects of

quality control that are jeopardized when a single laboratory controls all diagnostic testing for a disease gene.

24. Gene patents can directly interfere with our ability to investigate complex diseases. It is the case with most diseases that multiple genes play a causative role. For example, more than ten genes have thus far been associated with autism. Microarray technologies have brought us the ability to examine multiple genes at one time. But if one or more of these genes is patented, we are not able to develop a comprehensive, cost-efficient test for the full panel of genes.

25. Similarly, BRCA1 and BRCA2 may be associated with cancers other than breast and ovarian cancer, or even other diseases. But so long as the patents on these genes remain, no one will be able to include these genes in tests for other disease predispositions.

26. Gene sequencing involves purifying the DNA from the body and from at least some surrounding cellular material and making copies of the gene of interest, but the resultant sequence is functionally identical to the sequence that nature made in the body. The alterations or mutations in the gene that we are able to identify after sequencing the gene were made by nature, not by the process of sequencing or by me or other scientists, and the effect of those alterations or mutations is dictated by nature, not by any scientist.

27. Genes are products of nature and not inventions of man. They are so basic to science that any restriction that prevents scientists from looking

at the genes themselves or examining the effects of the genes is fundamentally inconsistent with the advancement of human knowledge.

28. There is absolutely no need for patent protection in the diagnostic field of use. For any disease gene identified, there are a large number of academic and private diagnostic laboratories prepared to establish clinical testing at very modest investment, which will increase access to clinical testing services, and provide incentives for test improvement in the form of greater sensitivity and cost-effectiveness.

I declare, pursuant to 28 U.S.C. §1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ David H. Ledbetter

David H. Ledbetter, Ph.D.

Executed on August 20, 2009

EXHIBIT 1

[Exhibit 1 Omitted]

[Declaration of Christopher Mason, filed August 26, 2009] [Caption Omitted In Printing] [Exhibit 1 Omitted]

I, Christopher E. Mason, declare under penalty of perjury:

1. I am a post-doctoral associate in the Program on Neurogenetics at Yale University. I am also the Visiting Fellow in Genomics, Ethics and Law of the Information Society Project at Yale Law School and a lecturer at the Law School.

2. I received a BS from the University of Wisconsin in 2001, a Masters degree from Yale in 2003, and a PhD from Yale in 2006. In each case, my area of study has been genetics.

3. I have written widely on the subject of genetics, publishing approximately 20 papers. For many of those papers, I was principal author. All were published in peer-reviewed journals such as Science, Genome Research, American Journal of Medical Genetics, Neurogenetics, and Human Mutation. I have also lectured all over the world on the subject of genetics. A copy of my curriculum vitae is attached.

4. The human genome is a three billion letter recipe for the creation of a human being, from a single-celled embryo to the 10 trillion cells of an adult. The genome of each human being is contained within almost every cell in the body. It defines obvious traits such as skin tone, eye color, and sex, but also directs the manifestation of very complex traits such as obesity, diabetes, Alzheimer's, or bipolar disorder.

5. Within the nucleus of human cells, the genome is found in tightly wound strands of DNA that merge with multiple proteins to form 46 chromosomes (23 inherited from mother and 23 inherited from father). This is the double-helix structure made famous by Watson and Crick.

6. The genome is composed of proteins and DNA. The DNA is the information content of the genome. DNA is made from four different nucleic acids: Adenosine (A), Cytosine (C), Guanine (G), and Thymine (T). Thus, each of the DNA strands consists essentially of a long string of these nucleic acids, represented by the four letters.

7. Smaller pieces of the DNA on each chromosome have been shown to create the proteins that the body uses for many of its functions. These smaller pieces are called genes. They are represented by certain combinations of these letters (A, C, G, and T) and are the specific instructions and actions of the genome.

8. The concept of a gene has existed since the 19th century. Gregor Mendel, in his experiments with pea plants, showed that certain traits are passed on as discrete entities, and do not appear blended in offspring. Mendel hypothesized that it was the assortment of these factors —called the genotype — that determined the appearance of the plants — the phenotype.

9. In 1909, Mendel's hidden unit of inheritance was called the "gene." Yet, the gene remained an abstract concept until 1915, when it was shown that genes corresponded to physical spans of chromosomal material. In 1941, George Beadle and Edward Tatum

proposed the 'one gene, one enzyme' hypothesis. This hypothesis stated that each individual gene gives rise to a single protein which in turn carries out a distinct biochemical function in the cell. A subsequent series of experiments revealed that the genes on chromosomes were made of DNA. In 1953, James Watson and Francis Crick discovered the double-helix structure of the DNA molecule.

10. Francis Crick continued decrypting the genetic code and proposed "the central dogma" of molecular biology: (1) information is encoded in DNA, (2) expressed as a copy called RNA, then (3) translated to eventually create a functional protein. In this scheme, a gene is a defined span of chromosomal DNA. In this central dogma, an active gene undergoes transcription and translation.

11. In transcription, DNA strands are unwound inside the body and the region that is the gene creates a temporary copy of itself called a messenger RNA (mRNA). This mRNA is initially very long and contains regions that need to be spliced out (introns) and regions that remain as part of the transcript (exons). The spliced mRNA is then finished by adding a cap on the beginning (5' G Cap) and a protective tail at the end (polyA tail). All of these process are done by the body and the order and actions are dictated by nature. The introns are removed by the body as a natural process because they will not be necessary for creation of a protein. The body ensures that the exons remain because they will be necessary for creation of a protein.

12. Translation is the process of converting the processed mRNA into a protein. This occurs at the ribosome of the cell. The ribosome converts tri-

nucleotide segments (codons) into amino acids, which create the poly-peptide (protein). In other words, the DNA represented by three letters (called a tri-nucleotide or a codon) create a single amino acid. The amino acids, when linked together, create a protein and the protein does the work of the body.

13. Genes are represented by letters corresponding to nucleic acids. This is referred to as the gene sequence. A gene sequence is generally hundreds or thousands of letters long and looks like GATCGCATG.... The process by which scientists or clinicians identify the sequence of a particular gene is called gene sequencing and is described below.

14. Except for identical twins, no two humans are genetically the same. Variation in the human genome is very common, and each person is estimated to be 99.5% similar, or to have five differences every 1000 base pairs (bp). The longest form of the BRCA gene is approximately 80,000bp, meaning that each person possesses at least 400 points of genetic variation in this gene.

15. Large scale variation can occur in the genome, such as the addition or deletion of substantial chromosomal regions. Thus, a particular gene may omit several hundred letters at one point or may add several hundred letters where they do not normally exist.

16. Small scale variation can also occur, manifested as slight sequence differences between the same genes in different individuals. Thus, for example, a sequence of a gene represented by ...GACTCG... might contain a variation that omits the first C (GATCG) or that adds an extra C at that

point (GACCTCG) or that reverses the order of two of the letters (CCATCG).

17. Scientists often refer to the "wild-type" or "normal" gene, which is the gene without variations. However, the notion that there exists a gene without variations is increasingly misleading. Newfound recognition of the high frequency of variation between individuals has implications for the definition (and patenting) of genes: such variation reinforces the emerging idea that no single DNA sequence can adequately capture either the human genome or a single gene, both of which occur naturally in a variety of forms.

18. Molecular characterization of genomes has already revealed substantial variation between normal human individuals in the form of chromosomal abnormalities. These structural variants are now believed to cover as much as 12% of the human genome. Thus, in any given individual, some tens of millions of nucleotides can be missing or duplicated with respect to the publicly available reference (or "wild-type") sequence. These extra copies or missing copies of the genome that are larger than 1000bp are called copy number variants (CNVs).

19. Some variants appear to have little or no effect on the body's processes. There are also variants whose significance is currently unknown. Other variants appear to correlate with an increased risk of particular diseases. These variants are called mutations. If a mutation exists in enough people (>5% of the population), they are called polymorphisms.

20. For example, certain mutations in the genes at issue in this case have been correlated with an increased risk of breast and/or ovarian cancer. These mutations were created by nature. The correlations between the mutations and the increased risk of disease are created by nature.

21. Because nature dictates that certain mutations increase the risk of disease, it is informative to sequence an individual's gene and determine if the mutation exists in one or both alleles, and if the person is carrying a mutant allele.

22. Labs and scientists sequence genes on a daily basis all over the world. Thousands of people have the technical knowledge and skill to sequence a gene, and now there are dozens of companies offering whole genome sequencing.

23. Once a gene has been sequenced, the result is the string of letters (bp). The letters are then examined to see if the mutation exists. In other words, the process of sequencing is designed simply to illuminate the information that nature has dictated in that person's genome. In that respect, sequencing is essentially no different than looking at something through a microscope. It takes something created by nature but too small to be seen and makes it visible.

24. There are a number of ways to sequence a gene. The first complete human genome was sequenced by the Human Genome Project. The main method of the Human Genome Project and the main method for most scientists still, is PCR (Polymerase Chain Reaction)-based amplification.

25. To sequence a gene, there are two main methods. PCR-amplification of the targeted gene or molecular cloning of a transformed eukaryotic host cell. Most scientists today use PCR-based methods to examine heritable (germline) genetic alterations and the germline sequence. However, these same methods can be used to examine non-heritable (somatic) changes; the source of DNA is what determines the difference.

26. For PCR-based amplification of a gene, primers are designed that flank the sequence of the gene, and a template DNA is required (for example, from a human patient). For this reaction to occur, the gene must first be taken out of the body and the DNA strands isolated. This is done by lysing (breaking open) the cells through sonication, removal of membranes by adding a detergent, removing proteins with a digestive enzyme, and then precipitating (condensing) the DNA in alcohol.

27. Another way to extract the DNA from a sample is by reverse transcription. In this process, the mRNA from cells are isolated and converted back into DNA for subsequent sequencing.

28. Reverse transcription of RNA depends upon having processed mRNAs. Mature mRNAs lack all the introns (have been spliced). They also have a long poly-adenosine (polyA) tail, and so the transcripts can be bound and isolated by pushing them through a column packed with complementary polyT sequences. Once isolated, the single-stranded mRNAs serve as a template in a reaction to create the complementary sequence, using an enzyme called reverse transcriptase. This creates the

complementary DNA (cDNA) of the RNA, which can then be sequenced on machines that sequence DNA.

29. cDNA does not exist in the body in the resultant form. However, cDNA is simply a mirror of the RNA which does exist in the body. In other words, as with the RNA, introns have been removed. The letter order is no longer that of the RNA but of its mirror. In other words, in the body, certain of the nucleotides, represented by the letters, always bind or attach to certain other nucleotides or letters. G always links to C and A always links to T. If the RNA in the body is a *G*, then the cDNA in the lab is a C. Knowing that the cDNA is a C tells you without exception that the RNA was a G. An alternative way of looking at this is to compare the cDNA with the original DNA. In this case, because the RNA was a mirror of the DNA, the cDNA is again identical to the DNA. The only difference is the introns have been removed. Thus, the functional sequence of the cDNA is identical to the functional sequence of the DNA.

30. To sequence DNA, researchers usually use dye-terminator methods, where a single-stranded DNA template is annealed to an oligonucleotide primer, extended using DNA polymerase, and then monitored by cameras. Each of the four bases (A,C,G,T) has a specific fluorescent dye that absorbs and emits light as the bases are integrated into the new strand of DNA, producing a chromatogram that indicates the sequence present in the template.

31. I have personally sequenced genes.

32. Regardless of the technique used to sequence the gene, the resultant string of letters is useful only insofar as it illuminates the sequence found in the

body. The informational and functional content of the sequence produced as a result of any of these techniques is identical to the sequence in the body. Thus, even though the structure of cDNA does not exist in precisely the same form in the body, for literally all practical and information-based purposes it is identical to that in the body. In addition, the sequence even of the cDNA is dictated not by scientists but by nature. And, as noted, the significance of that sequence, including its relationship to any disease, is dictated by nature.

33. As a product of nature, the DNA should never have been awarded patent protection. As the cDNA is essentially equivalent to the DNA, and was found using established methods, patents claims of the cDNA should also be rejected.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Christopher Mason

Executed 8/20, 2009 Christopher Mason

[Declaration of Elsa W. Reich, filed August 26, 2009] [Caption Omitted In Printing] [Exhibit 1 Omitted]

1. My name is Elsa W. Reich. I am a professor in the Human Genetics Program in the Department of Pediatrics at New York University School of Medicine. I am also a board certified genetic counselor. I am one of the plaintiffs in this action.

2. I received my B.S. in biology from the University of Chicago in 1956 and my M.S. in Human Genetics and Genetic Counseling from Sarah Lawrence College in 1974. I was certified by the American Board of Medical Genetics in Genetic Counseling in 1982 and by the American Board of Genetic Counseling in 1993 and recertified in 2006. I was appointed Professor (clinical) of Pediatrics in the Human Genetics Program in the New York University School of Medicine Department of Pediatrics in 2003. I have been a genetic counselor at New York University School of Medicine since 1974. I have co-authored published articles in the field of genetic counseling in various scientific journals including *Human Genetics* and *American Journal of Human Genetics*. I am a member of the American College of Medical Genetics, an organization that is also a plaintiff in this action. A copy of my curriculum vitae is attached hereto as Exhibit 1.

3. As a genetic counselor, I provide risk assessment and information to women and men about the probability of their having a heritable form of cancer in themselves or their families and advise them on the potential utility of obtaining an analysis of their genes to determine if they have genetic

mutations that correlate with an increased risk of developing breast or ovarian cancer or potentially other malignancies as well. Specifically, the genes of most interest to be analyzed are known as the BRCA1 and BRCA2 genes. If a woman/man requests this testing, I arrange for the analysis and provide an extensive explanation about the significance of the results. The only provider currently available to me to perform such analysis is Myriad Genetics. This is not because of the high level of difficulty of the test, but instead it is because Myriad Genetics holds certain patents relating to BRCA1 and BRCA2 and has asserted those patents in a continuous and systemic way that has foreclosed any other provider from offering such analysis to me and my patients.

4. From July 1, 2008 until June 30, 2009, Myriad has tested the genetic samples of approximately 350-400 patients whom I have counseled and who have elected genetic testing. The vast majority of these patients reside in New York.

5. As part of my daily responsibilities, I am in regular contact with geneticists, genetic counselors and lab employees. We have regularly discussed the fact that I can only use Myriad for BRCA1 and BRCA2 testing and the harm that this monopolization causes. Despite the fact that many of these geneticists and their labs could perform this same testing, they have not offered such testing because it is widely known in the field that doing so would, according to Myriad, violate its patents.

6. It is my belief that Myriad's continuous and systematic assertion of its BRCA patents has resulted in the elimination and prevention of other genetic testing options available to me and my

patients that could be cheaper, more appropriate, or useful as a source of a second opinion on Myriad's results for any given patient.

7. If I learned that the BRCA patents owned by Myriad were invalidated, I would potentially alter my testing choices in numerous ways.

8. First, I would send genetic samples from patients who are appropriate candidates for BRCA gene analysis and whose genes have not previously been screened to laboratories other than or in addition to Myriad Genetics. This is not merely a hypothetical possibility, as I understand that several laboratories, including those of my co-plaintiffs Drs. Chung, Ostrer and Ledbetter, have the capability and desire to provide such service as soon as the risk of patent infringement allegations is eliminated. To be precise, Dr. Ostrer is my colleague at NYU and I know personally that his lab has the capability and desire to provide such testing services to our patients. I would use these and other alternate labs for several reasons, including cost efficiency because it is my belief that once the patents are removed as a barrier to other labs providing BRCA testing, other labs would compete with Myriad, resulting in a lower price for the test. For other genetic testing, where there is more than one lab providing the test, I select the laboratory offering a lower cost providing that the testing is at least comparable in quality. This reduced cost could potentially give patients whose insurance companies do not pay for testing and who cannot otherwise afford to pay out of pocket for BRCA testing access to the service that they currently do not have.

9. Second, for some of my patients whose genetic samples have already been screened by Myriad, I might have genetic samples tested again by one of the alternate laboratories. In certain cases it may be important for a patient to obtain a second analysis, *e.g.*, if Myriad states that there is a mutation that creates an increased susceptibility to breast and ovarian cancer. For example, a woman contemplating surgical removal of her breasts or ovaries as a risk-reducing measure may wish to verify that she does indeed have a harmful mutation. I counseled such a patient recently and although she was prepared to undergo surgery once it was determined conclusively that she had a mutation, the single positive test result that Myriad provided did not provide her with the confidence level she needed; yet she was unable to obtain a confirming opinion from an independent laboratory.

10. Third, I might exercise more discretion over the methodology used in each patient's BRCA testing. There are several ways to screen for BRCA mutations. Myriad offers four alternatives:

A. The test most commonly utilized is "Comprehensive BRCAnalysis" which includes full sequencing of both genes as well as detection of five common rearrangements of BRCA 1.

B. The second test may target a single mutation that has previously been identified in the family and the care provider may elect to test only for that single mutation.

C. A third test, also a targeted mutation analysis, identifies the founder mutations that can be identified in certain populations that account for a large fraction of all of the mutations within that population. For example, among Ashkenazi Jews, there are three such "founder" mutations. When one of these founder mutations has been identified in a family, the testing of family members by convention includes testing for all three founder mutations. These three mutations account for 90-95% of all mutations identified in BRCA1 and 2 in this population and as the result the majority of Ashkenazi Jews do not require full sequencing which is many fold more expensive. Among individuals from Iceland, there is a single founder mutation which would also be targeted initially before any other testing.

D. BRACAnalysis Rearrangement Test or BART, detects large duplications and deletions which are not identified by full sequencing or by any other testing described above. This test is automatically added to the sequencing if a patient's family history, according to Myriad, fulfills specific criteria. I, along with many other counselors, would like to have this testing included in the standard "sequencing" testing. It is not always possible to provide all of the information that would assure that this test was included. That should be the providers' judgment. In addition, many insurers do not cover this test when it is and "add-on" and not included by the laboratory and even when the provider believes that it could potentially be informative, the patient may have to pay several hundred dollars out of pocket.

11. There are other methodologies that a lab might employ to screen for mutations; the extent of the testing described above is what Myriad has decided to offer. By allowing independent labs to perform BRCA related testing, alternative methods could be developed and utilized.

12. The methodology that is appropriate for a given patient depends upon her/his individual circumstances. For example, due to its high cost, with some exceptions, I do not recommend full sequencing for a patient with a known family history of a mutation in one of the BRCA genes for which a targeted and less expensive analysis exists. I am committed, together with my primary concern for the patient and my ability to provide him/her with the most extensive and sensitive testing available that is applicable to the patient, to decreasing the cost to patients as well as to insurers. I do not believe in providing a more expensive test solely because the insurer will reimburse the costs.

13. I believe that once multiple laboratories are performing BRCA testing, additional tests may be developed that will allow patients who must currently pay for full sequencing to instead take advantage of new targeted analyses that screen specific areas on the BRCA 1 and BRCA2 genes other than those currently tested by targeted analyses and that the costs will become more competitive.

14. I have the immediate capability and desire to undertake the activities described above. The only reason why I cannot do so today is a result of

Myriad's assertion of its BRCA related patents in a way that has foreclosed any other lab from providing BRCA genetic testing.

15. I have the desire and capability to immediately do each of these things. The only reason I am not doing so today is because of the monopolization of the market fc BRCA-related genetic testing by Myriad that has resulted from its assertion of its gene patents.

I declare, pursuant to 28 U.S.C. §1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Elsa Reich

Executed on August 21, 2009 Elsa W. Reich, MS

EXHIBIT 1

[EXHIBIT 1 OMITTED]

[Declaration of Shobita Parthasarathy, filed August 26, 2009] [Caption Omitted In Printing] [Exhibit 1 Omitted]

I, Shobita Parthasarathy declare under penalty of perjury:

1. I am currently an Assistant Professor of Public Policy and Co-Director of the Science, Technology, and Public Policy Program at the University of Michigan's Gerald R. Ford School of Public Policy.

2. My research focuses on comparative and international politics of genetics and biotechnology; the patentability of human biotechnology such as genes and stem cells; regulation of genetic medicine; the roles of patient advocacy groups; and the relationship between science and democracy.

3. I teach courses in genetics and biotechnology policy, science and technology policy analysis, and political strategy.

4. I received my undergraduate degree in Biology from the University of Chicago and M.A. and Ph.D. degrees in Science and Technology Studies from Cornell University. I have held postdoctoral fellowships at Northwestern University, University of California, Los Angeles, and the University of Cambridge. During the 2007-2008 academic year, I was awarded fellowships from the Woodrow Wilson International Center for Scholars in Washington, D.C., the American Council of Learned Societies, and the Max Planck Institute for Intellectual Property, Competition, and Tax Law in Munich, Germany. Further details of my background are contained in my current curriculum vitae, attached as an Exhibit.

5. In 2007, I published a book entitled *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care* (Cambridge, MA: MIT Press), which traces the development and deployment of genetic testing for breast and ovarian cancer (BRCA testing) in the United States and Britain. The book describes the history around the patenting of BRCA1 and BRCA2 and the ways in which the patenting of the genes impacted the commercialization of the test and allowed for one company, Myriad Genetics, to become the sole provider of BRCA testing in the United States.

6. I began the research for *Building Genetic Medicine* in 1998. In addition to an extensive review of the published literature, I conducted interviews both in the United States and Europe of all of the major stakeholders in the development of BRCA testing. These included the scientists who were involved in researching and finding the BRCA genes, officials at each of the institutions that developed BRCA testing, health care professionals at genetics clinics providing genetic testing, patent office officials, bioethicists and activists who commented on the patenting of the genes and development of the testing, and journalists and authors who had followed these developments. Overall, I interviewed 111 individuals in the United States, Britain, Belgium, Germany and The Netherlands. I also did archival research, and conducted ethnographic observation and scientific, medical, legal, and policy meetings, related to the history and contemporary politics of breast and ovarian cancer genetic science and technology in the US and Europe.

7. My current research focuses on the development of contemporary controversies over patenting biotechnology in the United States and Europe, with special focus on the patenting of living organisms and traditional knowledge.

8. Breast cancer is the most frequently diagnosed cancer worldwide. and is heavily publicized as the leading cause of cancer death for women in Britain and the second leading cause of cancer death for women in the United States. Ovarian cancer is the eighth most common cancer in women and causes more deaths in the Western world than any other gynecologic cancer. While considerable funding on the part of governments and medical charities has been dedicated to look for a cause and to develop prevention and treatment strategies for these diseases, neither an unequivocal cause nor a completely effective prevention, detection or treatment strategy has yet been found for either breast or ovarian cancer.

9. The BRCA genes are susceptibility genes, which means that individuals who have mutations in either the BRCA1 or BRCA2 genes have an increased risk, but not a certainty, of contracting breast and/or ovarian cancer during their lifetime.[1] Women with inherited BRCA1 mutations have from 3.2-85% cumulative risk of breast cancer, while women with

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[1] Nancie Petrucelli, Mary B. Daly, Julie O Bars Culver, and Gerald L. Feldman, "BRCA1 and BRCA2 Hereditary Breast/Ovarian Cancer—GeneReviews—NCBI Bookshelf," Website:
http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=brca1 , Downloaded August 24, 2009.

inherited BRCA2 mutations have from 4.6-86% cumulative risk of getting the disease. In the case of ovarian cancer, women with inherited BRCA1 mutations have a 40-52% cumulative risk, while women with inherited BRCA2 mutations have a 15-25% cumulative risk. Furthermore, only 5-10% of all breast and ovarian cancers are thought to be caused by a BRCA 1 or BRCA2 gene mutation. In sum, the relationship between mutations in the BRCA1 and BRCA2 genes and breast and ovarian cancer incidence is extremely complex.

10. Beginning in the 1970s, women began to articulate their discontent with treatments for breast cancer. By the 1980s, breast cancer patients had begun to mobilize in large numbers around the goals of increasing public and government attention to the breast cancer epidemic. Largely as a result of significant advocacy efforts on the part of organizations such as Breast Cancer Action (a plaintiff in this case) and the National Breast Cancer Coalition, in 1991 the US Department of Defense created a $210 million research program devoted to breast cancer research. The US government's funding for breast cancer research increased from less than $90 million in fiscal year 1990 to more than $2.1 billion by fiscal year 2008.[2]

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[2] National Breast Cancer Coalition, "Overview of NBCC/NBCCF's Major Accomplishments since its inception in 1991," Website: http://www.stopbreastcancer.org/index.php?option=com_content&task=view&id=259&Itemid=131, Downloaded: August 24, 2009.

11. The finding of the BRCA I and BRCA2 genes arose out of this context of increasing scientific, medical, and public interest in breast cancer. Starting in the 1980s, scientists from the United States, England, France, Germany, Japan, and other countries participated in what was often referred to as an international "race" to identify the nucleotide sequences linked to breast cancer. In 1989, various European and American research laboratories participated in the International Breast Cancer Linkage Consortium (the Consortium), and by 1990, they had achieved their first success, when a group of researchers led by Mary-Claire King at the University of California, Berkeley announced that they had determined that the Breast Cancer Susceptibility Gene 1 (BRCA 1), the first gene linked to breast cancer, was located on chromosome 17. Soon afterwards, research intensified as teams around the world focused in on this region of the genome. Multiple contenders emerged, including King, Mark Skolnick (co-founder of Myriad Genetics), and Mike Stratton (Institute for Cancer Research, London). In September 1994, a group led by scientists at Myriad Genetics and including researchers from the National Institute for Environmental Health Sciences (NIEHS), a subdivision of the National Institutes of Health (NIH), announced that they had sequenced the BRCA1 gene.

12. Many scientists believed there was at least one additional gene linked with breast cancer, and continued their research. In December 1995, a group of investigators led by Mike Stratton at Britain's Institute for Cancer Research announced that they had mapped and sequenced the BRCA2 gene, which

was linked to incidence of ovarian cancer and female and male breast cancer. Concerned that Myriad could gain a monopoly on research and testing on both BRCA genes and wanting to ensure that BRCA2 would remain in the public domain, Stratton's team applied for British and European patents covering the gene (eventually, they applied for patents in the US as well). The day before the Stratton group published the BRCA2 gene sequence in the scientific journal, *Nature*, however, Myriad announced that it too had found the gene and submitted its sequence to GenBank, an international depository of gene sequence information. It also applied for patents on the BRCA2 gene, in both the US and Europe.

13. Although both the Myriad Genetics and Stratton groups claimed priority in finding BRCA2, a citation network analysis, based on bibliometric data, demonstrates that the scientific community, worldwide, tends to believe that Mike Stratton and his colleagues mapped and sequenced the BRCA2 gene first.[3] Research has shown that scientists in the breast cancer genetics community tend to cite Stratton's *Nature* article announcing the BRCA gene sequence, as opposed to the article written by Myriad Genetics' scientists.

14. There has been considerable opposition to and controversy around Myriad's patents around the world. Many scientists have opposed the patents publicly, especially those from the cancer research

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[3] Robert Dalpé, Louise Bouchard, Anne-Julie Houle, and Louis Bédard, "Watching the Race to Find the Breast Cancer Genes," Science, Technology, and Human Values, 28: 187-216.

community in Britain, who felt especially aggrieved as a result of the BRCA2 controversy. They credited Mike Stratton, not Myriad, with finding the BRCA2 gene. Sir Walter Bodmer, a British scientist who had been involved in early research on the BRCA1 gene, said: "Myriad is claiming it contributed far more than it actually achieved. As a result...there is a lot of feeling of unfairness among British scientists."[4]

15. Myriad cannot claim to be the sole "inventor" of the BRCA genes, since uncovering the genes entailed a collective effort involving researchers, families with histories of breast and ovarian cancer who had contributed blood to research around the world, and studies done by multiple labs that contributed to the overall body of knowledge about breast cancer genetics. Not only did researchers who were not part of the Myriad-led team make important contributions (as noted above), but the Myriad-led team itself included important contributions from a variety of researchers.[5] The search for the BRCA 1 gene sequence was conducted by a team of forty-five researchers spread across the

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[4] Emma Ross, "Scientists object to gene patent," Guardian (London), January 17, 2000.

[5] Jordan Paradise, "European Opposition to Exclusive Control Over Predictive Breast Cancer Testing and the Inherent Implications for U.S. Patent Law and Public Policy: A Case Study of the Myriad Genetics' BRCA Patent Controversy," 59 Food & Drug Law Journal 133-154, 143 (2004) (citing Press Release, Institut Curie, The Key Dayes (Sept. 26, 2002), *available at* http://www.curie.fr/home/presse/actu_list.cfm/actu/presse/affaire/3lang/_fr.htrml (last visited Feb. 19, 2004)).

University of Utah, Myriad, Eli Lilly, McGill University in Montreal, and the National Institute of Environmental Health Sciences (NIEHS) in North Carolina.[6]

16. The six NIEHS researchers, who were funded by the National Institutes of Health (NIH), were initially excluded as co-inventors on the BRCA patents, and NIH was denied a share of the royalties.[7] NIH, however, argued that its NIEHS researchers conducted some of the most important work leading to the sequencing of the gene, including identifying the sequences of two of the BRCAI gene's fragments and helping "to cull vital pieces of genetic DNA and fit them together like a puzzle."[8] It filed a concurrent BRCA1 patent application, adding the names of its researchers as co-inventors, arguing that Myriad's patent applications were not complete and therefore were likely to be disallowed. Eventually, Myriad agreed to add the NIEHS inventors' names to their patent application, and NIH withdrew its application. Myriad also agreed to pay the NIEHS inventors royalties, but the NIEHS inventors had not received any payments as of 2005.

17. Oncormed, a company based in Gaithersburg, MD, applied for and received a patent on the "consensus sequence of the human BRCAI gene." The

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[6] Rachel Nowak, "NIH in Danger of Losing Out on BRCA1 Patent," 266 Science 209 (1994).

[7] Rachel Nowak, "NIH in Danger of Losing Out on BRCAI Patent," 266 Science 209 (1994).

[8] Associated Press, "U.S., Utah firm clash over rights to gene," The Salt Lake City Tribune, 29 October.

patent was issued in August 1997, four months prior to Myriad's first patent.

18. Significant federal funds were provided toward the finding of the BRCA genes. The National Institutes of Health funded a six-person NIEHS research team. NIH also provided approximately $2 million in research grants to the University of Utah.[9] According to sociology professor Jane S. Zones, the NIH "contributed one-third of the funding for BRCA1's discovery."[10]

19. In addition, the process of finding the genes was identical to that by which all other genes had been found. By the time the BRCA genes were found, that process was well-understood, widely used, and fairly uniform. Many researchers have pointed out that any scientist engaged in the process of looking for any gene would have followed a process similar to Myriad's. The British Society of Human Genetics argued in a formal statement: "The discovery of a gene sequence has for some little time been a well understood process. There is nothing novel or inventive about this in principle, and as such new gene sequences should not be patentable, even where a straightforward utility e.g., diagnostic testing has been specified, unless there has been real progress

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[9] Rachel Nowak, "NIH in danger of losing out on BRCA I patent," *Science* Vol. 266, October 14, 1994, p. 209.

[10] Jane S. Zones, "Profits from Pain: The Political Economy of Breast Cancer," In Breast Cancer: Society Shapes an Epidemic, edited by Anne S. Kasper and Susan J. Ferguson, New York: St. Martin's Press.

towards the design of a specific commercial product."[11]

20. Once the genes were discovered, medical professionals, genetics counselors, and patient advocates were very concerned about how testing for the BRCA genes would be developed. They knew that the genes only conferred an increased susceptibility of getting breast and/ovarian cancer, rather than a certainty of getting the disease, so counseling would be tricky. Furthermore, the only effective treatment for women with a BRCA gene mutation was prophylactic mastectomy, preventive removal of the breasts, which causes not only early menopause but also serious psychological effects. As a result, people worried about how testing would be provided, who would have access, and what kind of counseling they would receive.

21. A number of organizations issued recommendations on how they believed BRCA testing should be provided, including: American Society of Human Genetics, American Society of Clinical Oncology, American College of Obstetrics and Gynecology, American Medical Association, National Breast Cancer Coalition, and Breast Cancer Action. All of them encouraged the provision of testing in the context of counseling, and more research into the relationship between the gene mutations and disease incidence and the psychological and social implications of BRCA testing.

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[11] British Society of Human Genetics, "Patenting of Human Gene Sequnces and the EU Draft Directive," 1997.

22. Several laboratories in the United States were offering BRCA testing at the time that Myriad was awarded its patents. These included the University of Pennsylvania's Genetic Diagnostic Laboratory (GDL) and OncorMed, who both offered comprehensive testing of the genes. Together with Myriad, each of these laboratories offered its own approach to genetic testing for breast cancer as well. Because Myriad ultimately controlled patents on the BRCA genes, however, it was able to shut down these other providers—thus monopolizing diagnostic testing and dictating a single model for breast cancer genetic testing.

23. The University of Pennsylvania's GDL set up its testing services in 1995. As an academic laboratory, GDL's genetic testing services were guided by its dual priorities of research and healthcare. Starting in the early 1990s, the laboratory worked to develop a cheaper and faster alternative to DNA sequencing called *conformation sensitive gel electrophoresis (CSGE).* By 1993, the lab had established that CSGE could be a useful, and less expensive, alternative to full sequence analysis. In setting up its BRCA testing service, GDL followed many recommendations that were made by patient advocacy groups and professional organizations in offering BRCA testing in the context of its research and requiring all clients to undergo genetic counseling.

24. OncorMed, a medium-size start-up biotechnology company, was founded in 1993. As noted above, Oncormed had been actively involved in the BRCA gene discovery research, and developed its testing service based on its own patents and licenses

on the BRCA2 patents from Mike Stratton. Its licensing agreement with Stratton required the company to sublicense the patent further (to prevent a monopoly) and require counseling before and after undergoing genetic testing. Oncormed's approach to genetic testing focused on finding a gene mutation in high-risk families, so it was careful to require patients to provide family history information, in order to link the gene mutation information to the family history. It was also careful to minimize costs for patients by adopting a step-by-step testing process. The laboratory first searched for well-known, frequently occurring BRCA gene mutations. This test was priced at $500. If no mutations were found, it would then conduct protein truncation testing, which was said to be 80 percent sensitive, for unknown mutations in regions of the gene where mutations are most likely to be found. This test was priced at $800. If that test still resulted in no mutations, it would sequence the rest of the gene for another $800. Overall, this step-by-step approach was cheaper for patients and was also more efficient for the company.

25. Myriad Genetics adopted an approach to genetic testing that was considerably different from either GDL's or Oncormed's approach. Myriad, a start-up biotechnology company formed in 1991 by a scientists at the University of Utah, treated BRCA testing as a purely commercial service and as an ordinary medical test. After applying for patents on BRCA1 and BRCA2, Myriad set up its own BRCA testing service. Myriad considered issues of medical practice, such as how patients would be counseled and how results would be conveyed, as being outside of its scope, despite recommendations of patient

advocates and professional organizations that the best BRCA-testing systems would be those that provided counseling and were offered though research protocols. Its only requirement was that testing be provided through a physician, but it did not require a physician to have any specialized knowledge about genetic testing or counseling whatsoever. This is particularly problematic because research has shown that primary care physicians have little understanding of genetics and are less equipped to provide counseling than their specialist counterparts.[12]

26. Myriad offered four types of laboratory analyses very soon after it applied for patents on the BRCA genes: analysis of three mutations common among the Ashkenazi Jewish population (about $450); BRACAnalysis, which included full sequencing of the two genes (about $3,000); Rapid BRACAnalysis, which provided full sequencing with results returned to the physician within 7 days (about $4,000); and single mutation analysis (about $250), usually done after a mutation had been found in a family. Myriad's laboratory methods reflected its corporate priorities to reap immediate revenue from a testing service and to develop a database of information on fully sequenced BRCA genes that might eventually yield insight for therapeutic

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[12] M. Esther and A.-P. Sappino, "Primary care physicians' knowledge and attitudes towards genetic testing for breast-ovarian cancer predisposition," Annals of Oncology, 1131-1135.; A.N. Freedman, L. Wideroff, L. Olson, et al., "US physicians' attitudes toward genetic testing for cancer susceptibility." American Journal of Medical Genetics, 2003, 120(1): 63-71.

developments or could be sold or licensed to other companies.

27. By 1997, the US Patent and Trademark Office had granted both Oncormed and Myriad patents five patents covering various aspects of the BRCA1 gene sequence. In May 1998, following a series of lawsuits that settled out of court, Myriad bought OncorMed's patents and testing services for an undisclosed sum.

28. Armed with their patents and those it acquired from Oncormed, Myriad then sought to shut down the services of GDL as well as other remaining competitors. In early 1998, Myriad sent GDL a "cease and desist" letter, arguing that its services violated its BRCA patents by providing testing in return for payment. GDL resisted, arguing that it was only providing testing in research protocols that were exempt from Myriad's proprietary reach. Myriad disagreed, insisting that by giving results to, and receiving payments from, health-care professionals, GDL was providing a commercial service that violated its patents. GDL limited its testing service to individuals enrolled in research protocols within the National Cancer Institute's Cancer Genetics Network, a group of researchers funded by the National Institutes of Health. Myriad sent GDL another letter, stating that so long as GDL disclosed results to the patient, it was providing a commercial service rather than conducting research and violating Myriad's patent. After further negotiations, Myriad forced GDL to shut down its BRCA-testing laboratory. GDL could no longer conduct any tests (even for research purposes) that involved disclosure of results to the client. This resolution, which arose through a combination of Myriad's patent rights and

legal resources and GDL's reluctance to engage in a prolonged fight with the company, allowed Myriad to control not only the provision of BRCA testing, but also the definition of research and the boundary between research and commercial services for all those who engaged in laboratory or clinical services related to the BRCA genes. By holding patents on such fundamental findings (the BRCA genes), Myriad was able to define what counted as research and what counted as health care, and have significant influence over the kinds of studies that scientists were able to conduct. Imagine how the future of biotechnology would have been affected if Watson and Crick had decided to patent DNA and wield their patents in a similar manner.

29. Because Myriad has had a monopoly on BRCA testing in the United States, it has been able to control how it tests for the BRCA genes, and whether and how it incorporates new research findings into its testing system. For example, in 2001, researchers at the Institut Curie in France reported that they had found large cancer-causing rearrangements in the BRCA1 gene that were not being found through Myriad's testing system. Myriad initially refused to admit that its test was incomplete, and it eventually took years for the company to change its system and include analysis of these genomic rearrangements. In the interim, American clients undergoing BRCA testing assumed that Myriad's test was the "gold standard," and had no idea that the company was not analyzing these types of disease-causing genomic changes.

30. Today, Myriad's tests are available without the direct involvement of a physician or a specialized

genetic counselor. Since it shut down other major testing providers in the late 1990s, Myriad has partnered with companies that offer remote access to genetic testing services. DNA Direct, for example, allows clients to provide a sample through satellite blood-draw sites.[13] Blood samples are then sent to Myriad Genetics for testing (both full-sequence and mutation specific analyses are offered), and when results are available, clients can then review them online. This means that clients do not need to receive any type of counseling whatsoever, from any health care professional, when they undergo BRCA testing.

31. Myriad's patents on BRCA1 and BRCA2 have allowed it to monopolize clinical diagnostic BRCA testing in the United States. There are significant and obvious downsides to having a single laboratory offer a genetic diagnostic test. Women cannot get access to confirmatory testing, and the lack of competition does little to assure that the company will update its test to reflect the most up-to-date scientific knowledge or that the test will be offered at a reasonable price. Indeed, at least some of Myriad's competitors were offering testing services that were less expensive and more efficient than Myriad's test. Beyond this, clinical laboratory testing takes place in a broader context of patient care and services. By monopolizing the testing field, Myriad has also dictated the standards for patient care in breast cancer genetic testing. Other models for BRCA testing that existed prior to Myriad's assertion of its

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[13] "DNA Direct, "DNA Direct@DNAdirect.com," https://www.dnadirect.com/web/, retrieved August 23, 2009.

patents and included more comprehensive care, genetic counseling and an emphasis on research, are no longer available to women.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Shobita Parthasarathy
Shobita Parthasarathy

Executed on August 24th, 2009

EXHIBIT 1

[EXHIBIT 1 OMITTED]

[Declaration of Susan Love, MD, MBA, filed August 26, 2009] [Caption Omitted In Printing] [Exhibit 1 Omitted]

I, Susan M. Love, MD, MBA, declare under penalty of perjury:

1. I am currently a Clinical Professor of Surgery at the David Geffen School of Medicine at the University of California at Los Angeles ("UCLA"). I am also the President of the Dr. Susan Love Research Foundation, a nonprofit organization dedicated to the eradication of breast cancer. The Foundation conducts breast cancer research and also funds research through grant-making.

2. I submit this declaration in support of the plaintiffs in this case. Patents on the BRCA1 and BRCA2 human genes are obstacles to the clinical care of breast cancer patients and do not further the progress of medicine.

Background

3. I earned my Medical Degree from SUNY Downstate Medical Center in New York in 1974 and my Master's in Business Administration from UCLA in 1998. For more than thirty years, I have specialized in the treatment of breast cancer.

4. I am a member of numerous professional organizations, as noted fully in my curriculum vitae, which is attached. I am currently a Fellow at the American College of Surgeons and a member of the American Society of Breast Surgeons, the American Association for Cancer Research, the American Society Of Preventive Oncology and the Society for the Study of Breast Disease.

5. I was appointed by President Clinton to serve from 1998 to 2004 as a member of the National Cancer Advisory Board, which advises the Department of Health and Human Services and the National Cancer Institute about the Institute's activities and research. I also have served on the boards of many organizations that advocate on behalf of breast cancer patients, including the National Breast Cancer Coalition and the Young Survival Coalition.

6. I am the author of "Dr. Susan Love's Breast Book," which is widely considered the standard reference on all aspects of breast care and breast cancer. The first edition was published in 1990, and the fifth edition will be published next year.

7. My current research focuses on treatments for breast cancer and new methods for detection of risk. I am also investigating new approaches to connecting women and researchers to identify breast cancer causes and methods of prevention. In partnership with the Avon Foundation for Women, the Dr. Susan Love Research Foundation recently launched the Love/Avon Army of Women, which has two key goals: to recruit one million healthy women of every age and ethnicity, including breast cancer survivors and women at high-risk for the disease, to directly participate in breast cancer research; and to challenge the scientific community to expand its current focus to include breast cancer prevention research conducted on healthy women.

Effects of BRCA Gene Patents on Clinical Care of Breast Cancer Patients

8. I have treated thousands of women with breast cancer during my career. It is based on this experience that I have concluded that the patents granted over the BRCA1/2 genes impede clinical care.

9. As I understand it, the U.S. Patent and Trademark Office has granted patents over the BRCA1 and BRCA2 gene sequences, mutations along the genes, and the correlation between mutations and cancer. Because the patents are on the genes, and not on a particular test or device, the patent holder has the exclusive right to perform genetic testing and research on these genes in the United States.

10. All of us have BRCA1/2 genes. A small percentage of people have mutations that have been so far associated with cancer. Women who have BRCA1 or BRCA2 mutations have an elevated risk of breast cancer – anywhere between 50 to 80 percent – as well as a lifetime risk of ovarian cancer between 20 and 50 percent. Male carriers of mutations are also at increased risk of breast and prostate cancers. We are born with these genes and their mutations. The correlation between particular mutations with disease is a biological fact. None of this was invented by a human, and no patent on genetic sequences should prevent a doctor, scientist, or geneticist from analyzing or examining a person's genes.

11. BRCA1/2 genetic testing can provide vital information to a patient. She will not only learn her

risk for hereditary breast and ovarian cancer, but also can gain information that may be useful in determining prevention and treatment options. Some research has shown that people who test positive for a BRCA mutation can reduce their risk of cancer by participating in physical activity and avoiding obesity. Many women will opt for prophylactic mastectomy or oophorectomy, major surgeries that can cut risk. These are extremely difficult decisions for women, and those who are appropriate candidates for testing need timely information about their genetic status. Some women might opt for a lumpectomy before they receive their genetic test results, only to later decide to undergo a mastectomy when they find out they are positive for mutation. Women might decide to take hormonal therapy prior to finding out that they were carriers of a mutation suggesting that prophylactic oophorectomy might be a better choice. For women who have been diagnosed with cancer, recent studies have shown certain forms of chemotherapy may be more effective in targeting BRCA-mutated cells.[1] Because BRCA genetic status can dramatically affect a patient's decisions, it is important to ensure that patients have appropriate access to high quality timely BRCA genetic testing, as well as confirmatory testing.

12. BRCA genetic testing is one of the very few tests performed as part of breast cancer care and prevention for which a doctor or

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[1] Peter. C. Fong et al., Inhibition of Poly (ADP-Ribose) Polymerase in Tumors from BRCA Mutation Carriers, N. Engl.. J. Med. 2069;361 (July 9, 2009).

patient cannot get a second confirmatory test done through another laboratory. Access to second opinions and verification of results are integral to the standard of care that doctors must provide to their patients.

13. Increasingly, much of cancer research and treatment has focused on identifying the significance of a variety of biological characteristics of a tumor. These biomarkers can help determine the prognosis of a particular cancer, predict how a cancer will respond to a certain treatment, or both. Because so much of how we treat patients turns on an accurate identification of these biomarkers, it is crucial for patients and their doctors to be able to obtain second opinions and confirmatory testing.

14. When a patient is diagnosed with breast cancer, she can have a second pathologist examine the excised tumor to determine the type of cancer she has. The pathologist will analyze the tumor for characteristics such as size, type, rate of cell division, and whether the cancer has invaded blood vessels. Not infrequently, a second pathologist will change a diagnosis rendered elsewhere. This second opinion can be invaluable in determining the course of future treatment.

15. A patient can use more than one method of testing to find out whether her tumor is positive for estrogen receptors. This is the most common type of analysis we perform on tumors and helps resolve whether a patient should receive hormone blocking therapy.

16. Similarly, a patient can receive more than one test for the Her-2/neu receptor in a tumor. Her-2/neu

is an oncogene that contributes to cancer by telling cells to grow. Knowing whether a tumor is Her-2/neu positive is important, as positive tumors tend to be more aggressive and may respond differently than negative tumors to particular forms of drug therapy. Currently, there are at least two types of tests: one which measures the effect of overexpression of the Her-2/neu oncogene, whereas the second measures the cause of overexpression.

17. Imaging is done with MRI, bone scans, and xrays to determine whether the cancer may have spread. If a women were to have spread of her cancer to another organ, she is no longer curable and her whole treatment plan is changed. These images can and often are repeated when there is a question or undergo a secondary review to make sure the diagnosis is correct.

18. Just as a pathology report, an MRI, an estrogen receptor test, and a Her-2/neu receptor test structure a course of treatment, testing positive for a BRCA1/2 mutation can also be a significant factor in choosing the type of chemotherapy. Recent studies have shown that certain enzymes play a key role in repairing DNA.[2] Chemotherapy appears to be more effective in BRCA mutation carriers who are treated with a drug (known as a PARP inhibitor) that inhibits the DNA repair activity of these enzymes, because the drug prevents cancer cells from repairing DNA breaks and growing. Therefore, determining and confirming BRCA genetic status can be crucial to

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[2] Id.

deciding whether to administer a PARP inhibitor to a patient.

19. While access to testing and confirmatory testing are fundamental to breast cancer care, patents on the BRCA genes mean that these services are controlled by the patent holder. If the issue was simply that patents had been granted on a particular test, I believe that other laboratories would offer alternative tests. However, because the patents are on the genes, this is not a possibility. A patient in the U.S. cannot get full BRCA genetic sequencing done at a laboratory other than Myriad Genetics, which controls the patent rights over the genes. As a physician, this is of great concern to me. When patents are granted over genes, the patent holder can dictate how those genes are used in medicine and research — whether a test is offered, what test is performed (which mutations are looked for and which are not), the interpretation of test results, the cost of the test, and the research that is done. It is my professional opinion that genes are so fundamental to science, medicine, and clinical care that patents should not be granted so as to exclude doctors and geneticists from examining them. Allowing a company to control the BRCA1/2 genes is harmful to the quality of care we can provide our patients.

I declare, pursuant to 28 U.S.C. 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Susan Love

Susan Love

Executed on August 24th, 2009

EXHIBIT 1

[EXHIBIT 1 OMITTED]

[Declaration of Debra G.B. Leonard, M.D., Ph.D., filed August 26, 2009] [Caption Omitted In Printing] [Exhibit 1 Omitted]

1. My name is Debra G.B. Leonard, M.D., Ph.D. I am Professor of Pathology and Laboratory Medicine, Vice Chair for Laboratory Medicine and Director of the Clinical Laboratories in the Department of Pathology and Laboratory Medicine at Weill Cornell Medical College and New York-Presbyterian Hospital. I am also Chief Diversity Officer for Weill Cornell Medical College and head of the Office of Faculty Diversity in Medicine and Science.

2. I have been retained by the plaintiffs and their counsel as a consulting expert for this case. I have received no compensation for my services.

3. I received a B.A. in Biology in 1976 from Smith College, a Ph.D. in Biochemistry in 1987 from New York University, and an M.D. in 1988 from New York University School of Medicine. I completed my residency in Anatomic Pathology at New York University Medical Center in 1991. I completed a Surgical Pathology Fellowship at New York University Medical Center in 1992.

4. I have been employed in my current position since 2004. Prior to that, I was Assistant Professor in the Department of Pathology at Case Western Reserve University School of Medicine (1992-1996); and Assistant Professor (1996-2000) and Associate Professor (2000-2004) in the Department of Pathology and Laboratory Medicine at the University of Pennsylvania School of Medicine.

5. I am certified by the American Board of Pathology in Anatomic Pathology, and by the

American Boards of Pathology and Medical Genetics in Molecular Genetic Pathology.

6. I am a member of the College of American Pathologists and the Association for Molecular Pathology, two organizational plaintiffs in this case. I served as President of the Association for Molecular Pathology in 2000.

7. I am currently a member of the Institute of Medicine Round Table on Translating Genomic-based Research into Health, and chair of the Stakeholders Group of the CDC Program on Evaluating Genomic Applications in Practice and Prevention. I previously served as a member of the Advisory Committee on Genetics, Health and Society to Secretary of Health and Human Services Michael O. Leavitt.

8. I have spoken widely on various molecular pathology test services, the future of molecular diagnostics and the impact of gene patents on molecular pathology practice.

9. I am Editor of two textbooks of molecular pathology and have published more than 70 peer reviewed articles.

10. A copy of my curriculum vitae is attached hereto as an Exhibit.

IMPACTS OF GENE PATENTS ON MEDICAL PRACTICE

11. Gene patents have prevented me from practicing certain areas of my medical specialty, molecular genetic pathology.

12. I wanted to be a physician since I was 14 years old. My motivation was and remains a simple one: I

want to help people who are sick. To achieve this goal, I spent four years in college, seven in graduate school, and another four years in residency and fellowship.

13. Pathologists are the diagnostic detectives for clinicians who directly take care of patients. We are trained in clinical laboratory medicine and understand the appropriate use, performance, and interpretation of the tests that detect disease, predict outcomes, and direct therapies. My medical practice focuses on the appropriate use, performance, and interpretation of the tests that are based on molecular biology methods.

14. Patents on genes are preventing me from including the diagnosis of certain diseases in my medical practice. I can no longer perform testing for Canavan disease, Alzheimer disease, and Charcot-Marie-Tooth Type 1A disease because of patent enforcement. I have received "cease and desist" letters from companies holding patents on genes related to these and other diseases, stating that their patents give them exclusive rights to diagnostic testing for these diseases. Other physicians are prevented from testing for breast cancer genetic risk (BRCA1 and BRCA2). Studies have demonstrated the negative impact of gene patents for hereditary hemochromatosis mutations on the number of testing laboratories, in that almost 30% of laboratory directors stopped or did not develop hemochromatosis testing due at least in part to the patent on the hemochromatosis genetic sequence. Limiting the practice of physicians by patent law is not in the best interest of the public health.

15. Human genes and genetic sequences are products of nature. Those who patent genetic sequences and the correlation of genetic differences with the incidence or risk of a specific disease claim that they are not patenting part of the genome, since the patents claim only the cloned versions of the human sequence. But when I need to look at the same patented sequence in a patient to provide a diagnosis for her or his genetic disease, I cannot.

16. How do I explain to a patient that someone prevents me from looking at and characterizing a segment of her or his genome? The patient no longer has the ability to control her or his own body and the testing that can be done. How do I explain that I am not allowed by law to provide a test based on a part of her or his genome, a test that both the patient and her or his physician are asking me to perform, and that is necessary for diagnosis? Limiting the broad availability of medical testing is not in the best interest of the public health.

17. It makes perfect sense to me that patents should be granted on genetic diagnostic methods, such as that which was granted on PCR (polymerase chain reaction). But new uses claimed by disease gene patents for old methods of genetic diagnosis do not make sense. What is claimed when someone patents a gene is any use of any genetic diagnostic method for looking at that gene. This is like allowing the person with a patent on the microscope to claim, through patents, the use of the microscope to view each new small thing — the method of use would be the same, but where one looked and what one saw would vary. This does not make sense. The device was invented to view small items, and new use

patents should not be granted on each specific application thereof. Put another way, could the first person to view Pluto through a telescope patent the use of a telescope to view Pluto? Such use of the patent law is misaimed.

18. Anyone skilled in molecular biology has the knowledge and methods to sequence and examine any part of the human genome. Disease gene patents, including the patents on BRCA1 and BRCA2, limit where those skilled in these arts may look, based only on the fact that the patentee has identified an association between different chemical structures and risks of disease occurrence. This association is a natural phenomenon, and these patents essentially claim an observation of nature. Patents that restrict such fundamental knowledge about the human genome and about human disease are too broad.

19. Patents on correlations or associations between a gene sequence and a greater risk of disease allow the patent holder to control the use of that medical fact and information. In many cases, control of specific genetic information limits medical use of the information and impedes or prevents widespread research on the disease, the traditional pathway by which medical knowledge is advanced and shared. Limiting the use of medical information for research or medical practice is not in the best interest of the public health.

20. Gene patents are not necessary to further scientific discovery and the development of diagnostics, and these patents may in fact stifle needed clinical research. In a sense, disease gene patents are an end in themselves: these patents

cover genetic diagnostic testing. The underlying knowledge of genetic diversity and the role of genes in causing disease or disease susceptibility can often be put to clinical use immediately by well-known techniques without extensive development such as that necessary for pharmaceuticals. Market exclusivity as allowed by gene patents are not in the best interest of the public health.

21. Physicians in laboratory medicine do not require the incentives of gene patents to develop and provide genetic tests based on the published medical and scientific literature. Laboratories can rapidly translate new genetic knowledge into diagnostic tests for the benefit of patients without the need for the incentives and protection of patents. The driving force for those in the clinical laboratory is the need of the patient, based on calls from clinicians to the laboratory requesting that a test be performed on their patients. We do not check whether a patent has been filed before deciding to develop a diagnostic test based on the published literature, nor do we have the negotiating skills or financial resources for cross-licensing of the patented information required for the diagnostic test. Our motivation is the practice of medicine.

22. Much of the basic research that yields associations between genes and disease has been publicly funded. Most of the disease gene patents issued to date resulted from research performed by university-based clinician-researchers with funding provided at least in part by the federal government. A study I co-authored in 1997, soon after Myriad Genetics had obtained most of its patents on BRCA1 and BRCA2, showed that 63% of patents on gene

sequences resulted from federally supported research.

23. Some companies, including Myriad Genetics, have adopted a business model that aims to become the exclusive provider of a testing service. These companies identify patents needed for specific diagnostic tests before the patent even issues and negotiate an exclusive license for diagnostic testing based on the patent. In the meantime, the gene-disease association is published and clinical laboratories develop tests based on the genetic information. Once the patent issues, the laboratories that have developed the medical need and use for the test and are already performing it, are prevented from continuing to perform the test.

24. When a single provider of a health care service dominates the market, there is no competition for the price of testing, the quality of service, the method used for testing, the further refinement of the test, or access for the uninsured or those with health care coverage requiring that testing be done under contract. A sole provider of a medical service is not in the best interest of the public health.

*** [paragraphs omitted]

I declare, pursuant to 28 U.S.C. §1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Debra Leonard

Debra G.B. Leonard, M.D., Ph.D.

Executed on August 24th, 2009

EXHIBIT 1

[EXHIBIT 1 OMITTED]

[Exhibit 1 to Declaration of Daniel B. Ravicher, filed August 26, 2009] [Declaration Omitted]

Public Patent Foundation
Representing the Public's
Interest in the Patent
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August 11, 2009

Barry R. Satine, Esq.
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Re: Request for Waiver Of Claim Against Intended BRCA Activities

Dear Mr. Satine:

We represent several parties who have an immediate capability and desire to undertake certain activities relating to the BRCA1 and BRCA2 genes. Our clients and their intended activities are detailed below. We understand that your clients, Myriad Genetics, Inc. and Myriad Genetics Laboratories, Inc., (collectively "Myriad") claim to have patents that cover the BRCA1 and BRCA2 genes and related research and clinical activity. These patents include those specified in the pending litigation Association For Molecular Pathology et al v. United States Patent and Trademark Office et al., 1:09-cv-04515-RWS (SDNY).

By this letter, we request that Myriad expressly waive any claim for patent infringement against our clients for the below-identified activities. A failure to timely respond to this letter will be construed as indicating Myriad does not waive any such claim for patent infringement and in fact may very well assert claims of patent infringement against our clients should they undertake these intended activities. Construing Myriad's intentions in this way, our clients are unlikely to proceed with performing the identified activities, not because they lack the capability or desire to immediately do so, and not because they believe Myriad's patents are valid and would be infringed by the intended activity, but merely and solely because of a fear of subjecting themselves to the risk of being the target of patent infringement claims and the attendant burden that would come with responding to and defending against such claims.

Our clients and their intended activities are:

- The Association of Molecular Pathologists, American Society for Clinical Pathology, American College of Medical Genetics and College of American Pathologists are membership organizations with members who have the capability and desire to immediately begin engaging in research and clinical practice involving the BRCA I and BRCA2 genes.

Specifically, members of these organizations wish to immediately performing BRCA genetic testing services for the general public, including full sequencing of the BRCAI and BRCA2 genes, targeted mutation analysis and detecting large scale rearrangements.[1]

- Haig H. Kazazian, Jr., M.D., Arupa Ganguly, Ph.D., Wendy Chung, M.D., Ph.D., Harry Ostrer, M.D., David Ledbetter, Ph.D. and Steve Warren, Ph.D. are well known human geneticists who collectively and separately have the capability and desire to immediately begin or consider beginning (or in the case of at least Drs. Kazazian and Ganguly, resume or consider resuming) performing BRCAI and BRCA2 genetic testing for the general public for both research and clinical purposes. Such testing would include full sequencing of the BRCA1 and BRCA2 genes, targeted mutation analysis and detecting large scale rearrangements.

- Ellen Matloff, M.S. and Elsa W. Reich, M.S., C.G.C. are genetic counselors who have the capability and desire to immediately begin utilizing laboratories other than, or in addition to, Myriad, to perform BRCAI and BRCA2 genetic testing of their patients. Specific laboratories that have the immediate capability and desire to perform these services include those identified above.

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[1] We understand that some states may require analytical and clinical validity certification and approval before a lab may offer a new genetic test. To the extent such requirement applies, our clients have the capability and desire to immediately begin such certification and approval process so that they may then immediately begin performing BRCA clinical genetic testing.

- Breast Cancer Action is an organization that has the capability and desire to immediately (i) encourage researchers and clinicians to perform BRCA 1 and BRCA2 related activities, including BRCA 1 and BRCA2 genetic testing and research, and (ii) advertise the services of laboratories other than or in addition to Myriad, including specifically those identified above, to perform BRCA 1 and BRCA2 genetic testing services for the general public.

- Boston Women's Health Book Collective, Inc., dba Our Bodies Ourselves is an organization that has the capability and desire to immediately advertise the services of laboratories other than or in addition to Myriad, including specifically those identified above, to perform BRCA1 and BRCA2 genetic testing services for the general public.

- Kathleen Raker, Lisbeth Ceriani, Runi Limary, Patrice Fortune, Vicky Thomason and Genae Girard are individual women who have the capability and desire to immediately utilize laboratories other than or in addition to Myriad, including specifically those identified above, to receive BRCA1 and BRCA2 genetic testing.

Please confirm to us, within 7 days of this letter, that Myriad waives any claim for patent infringement against our clients for these intended activities. If Myriad needs more than 7 days to evaluate these issues, please at least confirm to us within 7 days of this letter that Myriad has initiated an investigation into the matter. And, of course, if there is any further information we can provide

Myriad about our clients and their intended activities, please do not hesitate to contact me at your earliest convenience.

If we do not receive a response from Myriad within 7 days of this letter, our clients will conclude that Myriad is now fully aware of their intended activities and has affirmatively chosen to not waive any potential claim of patent infringement it may have against them. It would then be reasonable for our clients to feel they would be at risk of having Myriad assert claims of patent infringement against them should they proceed to undertake the above identified activities that they have the immediate capability and desire to perform. Please note that this chilling effect clients necessarily believing any such claims would have merit, but instead is a result of the burden that responding to and defending against any such claims would place on them.

We look forward to receiving Myriad's response.

Sincerely,

/s/ Daniel B. Ravicher

Daniel B. Ravicher

[Exhibit 1 to Declaration of Barry R. Satine, filed September, 23, 2009] [Declaration Omitted]

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JP761862 August 18, 2009
625065-999001

VIA EMAIL AND US MAIL

Daniel B. Ravicher
Executive Director
Public Patent Foundation
Benjamin N. Cardozo School of Law
55 Fifth Avenue, Suite 928
New York, NY 10003

Dear Mr. Ravicher:

I am in receipt of your August 11, 2009 letter (the "Letter"). Let me begin by noting that your Letter erroneously states that Myriad Genetics Laboratories, Inc. is a client of my firm. It is not. If you wish to correspond with Myriad Genetics Laboratories, Inc., I suggest that you correspond with its General Counsel.

My firm does represent Myriad Genetics, Inc., which was named as a defendant in the litigation you commenced in the U.S. District Court for the Southern District of New York on behalf of the same 20 clients you identify in your Letter. As you know, my firm filed a motion to dismiss the complaint in that litigation because of your clients' lack of standing. If you have any opposition to that motion, it is due to be filed on August 26. Your Letter and your insistence on a pre-August 26 response to that Letter is a blatant and transparent attempt to create standing where none exists. As we pointed out in the memorandum of law in support of our motion, there is no standing because, among other things, there has been no action by any of the defendants that gives rise to a case or controversy with the plaintiffs. Your unilaterally sending the Letter to me changes nothing. Your clients still lack standing.

In order to ensure that this acknowledgment of your Letter is not misconstrued, let me explicitly state that we reject your attempt to force our client to choose between the options identified in your Letter, on the timetable set forth in your Letter. The Letter does little more than reiterate the allegations set forth in the complaint you filed in the above referenced litigation. We nonetheless will forward your Letter to our client.

Yours very truly,

Barry R. Satine

[Defendants' Answer, filed November 20, 2009]
[Caption Omitted In Printing]

ANSWER TO COMPLAINT

Defendants Myriad Genetics ("Myriad") and Lorris Betz, Roger Boyer, Jack Brittain, Arnold B. Combe, Raymond Gesteland, James U. Jensen, John Kendall Morris, Thomas Parks, David W. Pershing, and Michael K. Young in their official capacity, or alleged to have been named in their official capacity, as directors of the University of Utah Research Foundation (the "Directors") (collectively, Myriad and the Directors are referred to as the "Defendants"), by and through their undersigned counsel, respectfully submit this Answer to Plaintiffs' Complaint ("Complaint").

1. Defendants deny the allegations contained in paragraph 1, except to admit that human bodies contain genes and that genes can be inherited.

2. Defendants deny the allegations contained in paragraph 2, except to admit that the Complaint purports to assert causes of action with respect to United States Patent Numbers 6,033,857 (the "'857 patent"), 5,753,441 (the "'441 patent"), 5,837,492 (the "'492 patent"), 5,747,282 (the "'282 patent"), 5,710,001 (the "'001 patent"), 5,709,999 (the "'999 patent"), and 5,693,473 (the "'473 patent"), hereinafter referred to as the "Patents-in-Suit."

3. Defendants deny the allegations contained in paragraph 3, and respectfully refer to the claims of the Patents-in-Suit with respect to what "[t]he patents cover."

4. Defendants deny the allegations contained in paragraph 4.

5. Defendants deny the allegations contained in paragraph 5.

6. Defendants admit the allegations contained in paragraph 6.

7. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 7 and, therefore, deny them.

8. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 8 and, therefore, deny them.

9. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 9 and, therefore, deny them.

10. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 10 and, therefore, deny them.

11. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 11 with respect to Dr. Kazazian's employment and research activities and, therefore, deny them. Defendants deny the remaining allegations contained in paragraph 11.

12. Defendants deny the allegation contained in paragraph 12 that Dr. Kazazian received a cease-and-desist letter from defendant Myriad. Defendants

lack sufficient knowledge or information to form a belief as to the truth or falsity of the remaining allegations contained in paragraph 12 and, therefore, deny them.

13. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 13 with respect to Dr. Chung's employment and research activities and what she is ready, willing, and able to do and, therefore, deny them. Defendants deny the remaining allegations contained in paragraph 13.

14. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 14 with respect to Dr. Ostrer's employment and research activities and what he is ready, willing, and able to do and, therefore, deny them. Defendants deny the remaining allegations contained in paragraph 14.

15. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 15 with respect to Dr. Ledbetter's employment and research activities and what he is ready, willing, and able to do and, therefore, deny them. Defendants deny the remaining allegations contained in paragraph 15.

16. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 16 with respect to Dr. Warren's employment and research activities and what he is ready, willing, and able to do and, therefore, deny them. Defendants deny the remaining allegations contained in paragraph 16.

17. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 17 with respect to Ms. Matloff's employment and genetic counseling activities and what she is ready, willing, and able to do and, therefore, deny them. Defendants deny the remaining allegations contained in paragraph 17.

18. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 18 with respect to Ms. Reich's employment and genetic counseling activities and what she is ready, willing, and able to do and, therefore, deny them. Defendants deny the remaining allegations contained in paragraph 18.

19. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 19 and, therefore, deny them.

20. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 20 and, therefore, deny them.

21. Myriad admits the allegation contained in paragraph 21 that it received a sample submitted on behalf of Ms. Ceriani. Myriad denies the allegation contained in paragraph 21 that it will not accept MassHealth coverage. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the remaining allegations contained in paragraph 21 and, therefore, deny them.

22. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 22 and, therefore, deny them.

23. Myriad admits the allegation contained in paragraph 23 that it tested a sample from Ms. Girard and that the test result was positive for a deleterious mutation in the *BRCA*2 gene. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the remaining allegations contained in paragraph 23 and, therefore, deny them.

24. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 24 and, therefore, deny them.

25. Myriad admits the allegation contained in paragraph 25 that Ms. Thomason obtained *BRCA*1/*BRCA*2 genetic testing from Myriad in 2007 and was found to be negative for mutations covered by that test. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the remaining allegations contained in paragraph 25 and, therefore, deny them.

26. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 26 and, therefore, deny them.

27. Defendants admit the allegations contained in paragraph 27 that the United States Patent and Trademark Office is an agency of the Commerce Department of the United States and that its principal office is in Alexandria, Virginia. Defendants lack sufficient knowledge or information

to form a belief as to the truth or falsity of the remaining allegations contained in paragraph 27 and, therefore, deny them.

28. Defendants deny the allegations contained in paragraph 28, except to admit that Myriad is a for-profit corporation, that Myriad's principal place of business is in Salt Lake City, Utah, that Myriad is incorporated in Delaware, that Myriad formerly was a co-owner of some of the Patents-in-Suit, that Myriad is the exclusive licensee of the Patents-in-Suit, and that Myriad is the sole provider of full sequencing of *BRCA*1 and *BRCA*2 genes in the United States on a commercial basis.

29. Defendants deny the allegations contained in paragraph 29, except to admit that Lorris Betz, Roger Boyer, Jack Brittain, Arnold B. Combe, James U. Jensen, David W. Pershing, and Michael K. Young are Directors of the University of Utah Research Foundation, and that the University of Utah Research Foundation is an owner or part-owner of each of the Patents-in-Suit.

30. Defendants deny the allegations contained in paragraph 30, except to admit that Endo Recherche, Inc., of Sainte-Foy, Canada, HSC Research & Development Limited Partnership of Toronto, Canada, and the Trustees of the University of Pennsylvania are additional owners of the '492 patent and the '857 patent, and that the United States of America, as represented by the Secretary of the Department of Health and Human Services, is an additional owner of the '001 patent, the '441 patent, United States Patent No. 6,162,897, and the '282 patent.

31. Defendants deny the allegations contained in paragraph 31, except to admit that Myriad is the exclusive licensee of the Patents-in-Suit.

32. Defendants deny the allegations contained in paragraph 32, except to admit that Plaintiffs purport to challenge the following claims of the following patents: claims 1, 2, 5, and 6 of the '282 patent; claim 1 of the '492 patent; claim 1 of the '473 patent; claim 7 of the '282 patent; claims 6 and 7 of the '492 patent; claim 1 of the '999 patent; claim 1 of the '001 patent; claim 1 of the '441 patent; claims 1 and 2 of the '857 patent; and claim 20 of the '282 patent.

33. Defendants deny the allegations contained in paragraph 33, except to admit that every person's body is composed of cells.

34. Defendants deny the allegations contained in paragraph 34, except to admit that DNA is deoxyribonucleic acid.

35. Defendants deny the allegations contained in paragraph 35, except to admit that genetic sequences can vary and that such variations can be inherited or acquired during a lifetime.

36. Defendants deny the allegations contained in paragraph 36.

37. Defendants deny the allegations contained in paragraph 37, except to admit that *BRCA*1 and *BRCA*2 are human breast and ovarian cancer predisposing genes and that some alleles of these genes cause susceptibility to cancer, in particular, breast, ovarian, prostate and pancreatic cancer.

38. Defendants admit the allegations contained in paragraph 38.

39. Defendants deny the allegations contained in paragraph 39, except to admit that *BRCA*1 and *BRCA*2 are human breast and ovarian cancer predisposing genes and that some alleles of these genes cause susceptibility to cancer, in particular, breast and ovarian cancer.

40. Defendants deny the allegations contained in paragraph 40, except to admit that a *BRCA*1 and *BRCA*2 genetic test result can be a factor that a woman considers in making medical decisions.

41. Defendants deny the allegations contained in paragraph 41, except to admit that research was being done in the 1990's regarding a human breast and ovarian cancer predisposing gene.

42. Defendants deny the allegations contained in paragraph 42, except to admit that efforts to isolate the *BRCA*1 gene have proceeded since it was first mapped to chromosome 17 in 1990.

43. Defendants deny the allegations contained in paragraph 43.

44. Defendants deny the allegations contained in paragraph 44, except to admit that scientific research was being conducted for years to isolate and detect the human *BRCA*2 gene.

45. Defendants deny the allegations contained in paragraph 45, except to refer to the '857 and the '492 patents with respect to the techniques and methodology used to isolate and detect the human *BRCA*2 gene.

46. Defendants deny the allegations contained in paragraph 46.

47. Defendants deny the allegations contained in paragraph 47.

48. Defendants deny the allegations contained in paragraph 48.

49. Defendants deny the allegations contained in paragraph 49.

50. With respect to the allegations contained in paragraph 50, Defendants admit that the Patents-in-Suit were obtained from the United States Patent and Trademark Office pursuant to applicable laws and regulations. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the remaining allegations contained in paragraph 50 and, therefore, deny them.

51. Defendants deny the allegations contained in paragraph 51.

52. Defendants deny the allegations contained in paragraph 52.

53. With respect to the allegations contained in paragraph 53, Defendants admit that the Patents-in-Suit were obtained from the United States Patent and Trademark Office pursuant to applicable laws and regulations. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the remaining allegations contained in paragraph 53 and, therefore, deny them.

54. Defendants deny the allegations contained in paragraph 54.

55. Defendants deny the allegations contained in paragraph 55, except to refer to the claims of the Patents-in-Suit with respect to what "the claims in Myriad's patents cover."

56. Defendants deny the allegations contained in paragraph 56, except to refer to the '282 patent with respect to what claim 1 of the '282 patent "covers."

57. Defendants deny the allegations contained in paragraph 57, except to refer to the '282 patent with respect to what claim 2 of the '282 patent "covers."

58. Defendants deny the allegations contained in paragraph 58, except to refer to the '282 patent with respect to what claim 5 of the '282 patent "covers."

59. Defendants deny the allegations contained in paragraph 59, except to refer to the '282 patent with respect to what claim 6 of the '282 patent "covers."

60. Defendants deny the allegations contained in paragraph 60, except to refer to the '492 patent with respect to what claim 1 of the '492 patent "covers."

61. Defendants deny the allegations contained in paragraph 61, except to refer to the respective patents with respect to what claim 1 of the '473 patent, claim 7 of the '282 patent, and claims 6 and 7 of the '492 patent "claim."

62. Myriad denies the allegations contained in paragraph 62, except to refer to the Patents-in-Suit with respect to what activities the named inventors of the Patents-in-Suit performed. The Directors lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 62 and, therefore, deny them.

63. Defendants deny the allegations contained in paragraph 63, except to refer to the '473 patent with respect to what claim 1 of the '473 patent "claims."

64. Defendants deny the allegations contained in paragraph 64, except to refer to the '282 patent with respect to what claim 7 of the '282 patent "claims."

65. Defendants deny the allegations contained in paragraph 65, except to refer to the '492 patent with respect to what claim 6 of the '492 patent "covers."

66. Defendants deny the allegations contained in paragraph 66, except to refer to the '492 patent with respect to what claim 7 of the '492 patent "claims."

67. Defendants deny the allegations contained in paragraph 67, except to refer to the respective patents as to what claim 1 of the '473 patent, claim 7 of the '282 patent, and claims 6 and 7 of the '492 patent "include."

68. Defendants deny the allegations contained in paragraph 68.

69. Defendants deny the allegations contained in paragraph 69, except to refer to the '999 patent with respect to what claim 1 of the '999 patent "covers."

70. Defendants deny the allegations contained in paragraph 70.

71. Defendants deny the allegations contained in paragraph 71, except to refer to the Patents-in-Suit with respect to what the claims of the Patents-in-Suit "include."

72. Defendants deny the allegations contained in paragraph 72, except to refer to the '001 patent with respect to what claim 1 of the '001 patent "involves."

73. Defendants deny the allegations contained in paragraph 73, except to refer to the '441 patent with respect to what claim 1 of the '441 patent "covers."

74. Defendants deny the allegations contained in paragraph 74, except to refer to the '857 patent with respect to what claim 1 of the '857 patent "involves."

75. Defendants deny the allegations contained in paragraph 75, except to refer to the '857 patent with respect to what claim 2 of the '857 patent "involves."

76. Defendants deny the allegations contained in paragraph 76, except to refer to the '282 patent with respect to what claim 20 of the '282 patent "involves."

77. Defendants deny the allegations contained in paragraph 77, except to refer to the Patents-in-Suit with respect to what the claims of the Patents-in-Suit "include."

78. Defendants deny the allegations contained in paragraph 78, except to refer to the Patents-in-Suit with respect to what the claims of the Patents-in-Suit are "limited to."

79. Defendants deny the allegations contained in paragraph 79, except to refer to the Patents-in-Suit with respect to what activities the applicants of the Patents-in-Suit performed.

80. Defendants deny the allegations contained in paragraph 80, except to refer to the Patents-in-Suit with respect to what the claims of the Patents-in-Suit are "limited to."

81. Defendants deny the allegations contained in paragraph 81, except to admit that Myriad offers a test to assess a woman's risk of developing breast or ovarian cancer based on detection of mutations in the *BRCA*1 and *BRCA*2 genes.

82. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity

of the allegations contained in paragraph 82 and, therefore, deny them, except to admit that Myriad is the exclusive licensee of the Patents-in-Suit.

83. Defendants deny the allegations contained in paragraph 83.

84. Defendants deny the allegations contained in paragraph 84, except to admit that Myriad is the exclusive licensee of the Patents-in-Suit.

85. Defendants deny the allegations contained in paragraph 85, except to admit that Myriad is the exclusive licensee of the Patents-in-Suit.

86. Defendants deny the allegations contained in paragraph 86, except to admit that Myriad maintains a database of data relating to the *BRCA*1 and *BRCA*2 genes.

87. Defendants deny the allegations contained in paragraph 87.

88. Defendants deny the allegations contained in paragraph 88.

89. Defendants deny the allegations contained in paragraph 89.

90. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 90 with respect to Ms. Girard, Ms. Limary, and "any other women" and, therefore, deny them. Defendants deny the remaining allegations contained in paragraph 90, except to admit that Myriad is the exclusive licensee of the Patents-in-Suit.

91. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity

of the allegations contained in paragraph 91 with respect to "laboratories, such as that operated by Dr. Ledbetter" and, therefore, deny them. Defendants deny the remaining allegations contained in paragraph 91.

92. Defendants deny the allegations contained in paragraph 92, except to admit that the list price of Myriad's BRAC*Analysis*® test is more than $3,000.

93. Myriad denies the allegation in paragraph 93 that it will not accept the insurance of plaintiffs Ceriani and Fortune. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the remaining allegations contained in paragraph 93 and, therefore, deny them.

94. Defendants admit the allegation contained in paragraph 94 that Myriad offers a test called BRAC*Analysis*® Rearrangement Test (or "BART") that is designed to detect large rearrangements. Defendants further admit the allegations contained in paragraph 94 that Myriad will conduct BART testing for some women who meet its criteria at no additional cost and that other women must pay an additional price of approximately $650 for BART testing. Defendants deny the remaining allegations contained in paragraph 94.

95. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 95 with respect to the medical histories and advice given to "women, including plaintiffs Thomason and Raker" and, therefore, deny them. Defendants deny the remaining allegations contained in paragraph 95.

96. Defendants deny the allegations contained in paragraph 96.

97. Defendants deny the allegations contained in paragraph 97, except to admit that Myriad has not opposed non-commercial research related to the *BRCA*1 and *BRCA*2 genes.

98. Defendants deny the allegations contained in paragraph 98.

99. Defendants lack sufficient knowledge or information to form a belief as to the truth or falsity of the allegations contained in paragraph 99 with respect to the research activities of plaintiffs Dr. Chung and Dr. Ostrer and, therefore, deny them. Defendants deny the remaining allegations contained in paragraph 99.

100. Defendants deny the allegations contained in paragraph 100.

101. Defendants deny the allegations contained in paragraph 101.

102. Defendants deny the allegations contained in paragraph 102.

103. Defendants deny the allegations contained in paragraph 103.

104. To the extent any allegations are not addressed above, they are denied.

AFFIRMATIVE DEFENSES

i. This Court lacks subject-matter jurisdiction over this case.

ii. This Court lacks personal jurisdiction over the Directors.

iii. Plaintiffs' claims are barred by the doctrine of laches, waiver, and equitable estoppel.

iv. The Complaint fails to state a claim upon which relief can be granted.

DEFENDANTS' PRAYER FOR RELIEF

WHEREFORE, Defendants pray that the Court:

a. Dismiss the Complaint with prejudice;

b. Award Defendants attorney's fees and costs; and

c. Award Defendants such other and further relief as the Court may deem proper.

Dated: November 20, 2009

JONES DAY

By: /s/ Brian M. Poissant
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[Declaration of Richard Baer, filed December 23, 2009] [Caption Omitted In Printing] [Exhibit 1 omitted]

I, Richard Baer, declare under penalty of perjury:

1. I currently hold the following positions at Columbia University: Professor of Pathology & Cell Biology; Deputy Director, Institute for Cancer Genetics; and Assoc. Dir. for Basic Research, Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, Irving Cancer Research Center.

2. In 1976 I received a B.A. from Rutgers College in Biological Sciences. In 1981 I received a Ph.D. from Rutgers University in Microbiology. My post-doctoral research at the MRC-Laboratory of Molecular Biology (Cambridge, UK) and my subsequent work as an independent scientist has focused on the molecular biology of cancer. A copy of my *curriculum vitae* and a listing of my *BRCA1*-related publications are attached as Exhibits 1 & 2.

3. I began researching the *BRCA1* gene in 1994, not long after Myriad's landmark publication of the full-length *BRCA1* sequence. In research collaborations with over 90 different scientists since 1994 I have published 27 peer-reviewed articles on *BRCA1*. Of these 27 publications, 24 report my own original research while the other 3 review the voluminous research conducted by myself and others on *BRCA1*. I was aware that aspects of the BRCA genes were covered by Myriad's patent rights.

4. During my *BRCA1* research I have helped elucidate various physiological roles and properties of the *BRCA1* gene and the protein it encodes. For example:[1]

(a) We discovered and/or further elucidated several aspects of *BRCA1* itself, including: BRCA1's participation in DNA damage response (refs. 10, 16, 25); how BRCA1 expression is controlled during the cell-cycle (refs. 9, 19, 25); and how BRCA1 exerts its DNA damage repair effects (ref. 1).

(b) We discovered a novel gene, *BARD1*, and discovered that BRCA1 exerts its various effects in the cell in tandem with the BARD1 protein. (Ref. 26.)

(c) We discovered and/or further elucidated several aspects of the BRCA1/BARD1 heterodimer, including: the nuclear co-localization of BARD1 and BRCA1 (ref. 25); BARD1's role in nuclear retention of BRCA1 (ref. 13); the unique pattern of polyubiquitination catalyzed by the BARD1/BRCA1 heterodimer (ref. 11); the critical role BARD1 plays in BRCA1's homologous repair function (refs. 4, 10); the mechanism by which the BARD1/BRCA1 heterodimer mediates RNA processing (ref. 8); and the essential role of the BARD1/BRCA1 heterodimer in normal embryonic development (ref. 12) and in tumor suppression (ref. 2).

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[1] "Ref._" below refers to the indicated publication listed in the attached Exhibit 2.

(d) We discovered and/or further elucidated several aspects of *BARD1* itself, including: *BARD1*'s genomic structure (ref. 24); the association between *BARD1* mutation and breast, ovarian and endometrial cancers (ref. 24); the importance of BARD1 phosphorylation in DNA damage repair (ref. 7); and the way in which cancer-associated BARD1 mutations give rise to cancer (ref. 4).

(e) We discovered the interaction between the BRCA1 protein and CtIP, a protein involved in DNA damage responses and control of RNA transcription (refs. 22 and 19). We also contributed to studies implicating CtIP in cell cycle checkpoint control (ref. 6) and resection of double-strand DNA breaks (ref. 27).

5. My research involved, *inter alia*, plasmids containing *BRCA1* cDNA, heterologous cells expressing BRCA1 protein, primers designed to PCR amplify *BRCA1* cDNA, and antibodies against BRCA1 protein.

6. Until asked to prepare this declaration, I had never been contacted by Myriad Genetics, Inc. Neither the patents at issue in this suit nor Myriad Genetics, Inc., have in any way hampered my research.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Richard Baer
Richard Baer, Ph.D

Executed on December 7, 2009

EXHIBIT 1

[EXHIBIT 1 OMITTED]

EXHIBIT 2

LIST OF PUBLICATIONS RELATING TO BRCA1/BRCA2

1. Reid LJ, Shakya R, Modi AP, Lokshin M, Cheng JT, Jasin M, Baer R, Ludwig T. Proc Natl Acad Sci U S A. 2008 Dec 30;105(52):20876-81. Epub 2008 Dec 16. E3 ligase activity of BRCA1 is not essential for mammalian cell viability or homology-directed repair of double-strand DNA breaks ..

2. Shakya R, Szabolcs M, McCarthy E, Ospina E, Basso K, Nandula S, Murty V, Baer R, Ludwig T. Proc Natl Acad Sci U S A. 2008 May 13;105(19):7040-5. Epub 2008 Apr 28. The basal-like mammary carcinomas induced by Brca1 or Bard1 inactivation implicate the BRCA1/BARD1 heterodimer in tumor suppression.

3. Wu M, Soler DR, Abba MC, Nunez MI, Baer R, Hatzis C, Llombart-Cussac A, Llombart-Bosch A, Aldaz CM. Mol Cancer Res. 2007 Dec;5(12):1285-95. CtIP silencing as a novel mechanism of tamoxifen resistance in breast cancer.

4. Laufer M, Nandula SV, Modi AP, Wang S, Jasin M, Murty VV, Ludwig T, Baer R. J Biol Chem. 2007 Nov 23;282(47):34325-33. Epub 2007 Sep 11. Structural requirements for the BARD1 tumor suppressor in chromosomal stability and homology-directed DNA repair.

5. Lu Y, Amleh A, Sun J, Jin X, McCullough SD, Baer R, RenD, Li R, Hu Y. Mol Endocrinol. 2007 Mar;21(3):651-63. Epub 2006 Dec 21. Ubiquitination and proteasome-mediated degradation of BRCA1 and

BARD1 during steroidogenesis in human ovarian granulosa cells.

6. Yu X, Fu S, Lai M, Baer R, Chen J. Genes Dev. 2006 Jul 1;20(13):1721-6. BRCA1 ubiquitinates its phosphorylation-dependent binding partner CtIP.

7. Choudhury AD, Xu H, Modi AP, Zhang W, Ludwig T, Baer R. J Biol Chem. 2005 Jul 1;280(26):24669-79. Epub 2005 Apr 26. Hyperphosphorylation of the BARD1 tumor suppressor in mitotic cells.

8. Kleiman FE, Wu-Baer F, Fonseca D, Kaneko S, Baer R, Manley JL. Genes Dev. 2005 May 15;19(10):1227-37. BRCA1/BARD1 inhibition of mRNA 3' processing involves targeted degradation of RNA polymerase II.

9. Choudhury AD, Xu H, Baer R. J Biol Chem. 2004 Aug 6;279(32):33909-18. Epub 2004 May 27. Ubiquitination and proteasomal degradation of the BRCA1 tumor suppressor is regulated during cell cycle progression.

10. Westermark UK, Reyngold M, Olshen AB, Baer R, Jasin M, Moynahan ME. Mol Cell Biol. 2003 Nov;23(21):7926-36. BARD1 participates with BRCA1 in homology-directed repair of chromosome breaks.

11. Wu-Baer F, Lagrazon K, Yuan W, Baer R. J Biol Chem. 2003 Sep 12;278(37):34743-6. Epub 2003 Jul 30. The BRCA1/BARD1 heterodimer assembles polyubiquitin chains through an unconventional linkage involving lysine residue K6 of ubiquitin.

12. McCarthy EE, Celebi JT, Baer R, Ludwig T. Mol Cell Biol. 2003 Jul;23(14):5056-63. Loss of

Bard1, the heterodimeric partner of the Brca1 tumor suppressor, results in early embryonic lethality and chromosomal instability.

13. Fabbro M, Rodriguez JA, Baer R, Henderson BR. J Biol Chem. 2002 Jun 14;277(24):21315-24. Epub 2002 Mar 29. BARD1 induces BRCA1 intranuclear foci formation by increasing RING-dependent BRCA1 nuclear import and inhibiting BRCA1 nuclear export.

14. Baer R, Ludwig T. Curr Opin Genet Dev. 2002 Feb;12(1):86-91. Review. The BRCA1/BARD1 heterodimer, a tumor suppressor complex with ubiquitin E3 ligase activity.

15. Xu XL, Wu LC, Du F, Davis A, Peyton M, Tomizawa Y, Maitra A, Tomlinson G, Gazdar AF, Weissman BE, Bowcock AM, Baer R, Minna JD. Cancer Res. 2001 Nov 1;61(21):7943-9. Inactivation of human SRBC, located within the 11p15.5-p15.4 tumor suppressor region, in breast and lung cancers.

16. Wu-Baer F, Baer R. Nature. 2001 Nov 1;414(6859):36. Effect of DNA damage on a BRCA1 complex.

17. Baer R. Nat Struct Biol. 2001 Oct;8(10):822-4. Review. With the ends in sight: images from the BRCA1 tumor suppressor.

18. Yoshikawa K, Ogawa T, Baer R, Hemmi H, Honda K, Yamauchi A, Inamoto T, Ko K, Yazumi S, Motoda H, Kodama H, Noguchi S, Gazdar AF, Yamaoka Y, Takahashi R. Int J Cancer. 2000 Oct 1;88(1):28-36. Abnormal expression of BRCA1 and BRCA1-interactive DNA-repair proteins in breast carcinomas.

19. Yu X, Baer R. J Biol Chem. 2000 Jun 16;275(24):18541-9. Nuclear localization and cell cycle-specific expression of CtIP, a protein that associates with the BRCA1 tumor suppressor.

20. Ayi TC, Tsan JT, Hwang LY, Bowcock AM, Baer R. Oncogene. 1998 Oct 22;17(16):2143-8. Conservation of function and primary structure in the BRCA1-associated RING domain (BARD1) protein.

21. Baer R, Lee WH. J Mammary Gland Biol Neoplasia. 1998 Oct;3(4):403-12. Review. Functional domains of the BRCA1 and BRCA2 proteins.

22. Yu X, Wu LC, Bowcock AM, Aronheim A, Baer R. J Biol Chem. 1998 Sep 25;273(39):25388-92. The C-terminal (BRCT) domains of BRCA1 interact in vivo with CtIP, a protein implicated in the CtBP pathway of transcriptional repression.

23. Baer R. Breast Dis. 1998 Apr;10(1-2):23-32. Protein partners of the BRCA1 tumor suppressor.

24. Thai TH, Du F, Tsan JT, Jin Y, Phung A, Spillman MA, Massa HF, Muller CY, Ashfaq R, Mathis JM, Miller DS, Trask BJ, Baer R, Bowcock AM. Hum Mol Genet. 1998 Feb;7(2):195-202. Mutations in the BRCA1-associated RING domain (BARD1) gene in primary breast, ovarian and uterine cancers.

25. Jin Y, Xu XL, Yang MC, Wei F, Ayi TC, Bowcock AM, Baer R. Proc Natl Acad Sci U S A. 1997 Oct 28;94(22):12075-80. Cell cycle-dependent colocalization of BARD1 and BRCA1 proteins in discrete nuclear domains.

26. Wu LC, Wang ZW, Tsan JT, Spillman MA, Phung A, Xu XL, Yang MC, Hwang LY, Bowcock AM, Baer R. Nat Genet. 1996 Dec;14(4):430-40. Identification of a RING protein that can interact in vivo with the BRCA1 gene product.

27. Sartori AA, Lukas C, Coates J, Fu S, Baer R, Lukas J, Jackson SP. Nature 2007 450:509-514. CtIP cooperates with the MRE11 complex to promote DNA end resection.

[Declaration of Rong Li, filed December 23, 2011] [Caption Omitted In Printing] [Exhibit 1 omitted]

I, Rong Li, declare under penalty of perjury:

1. I currently hold several positions at the University of Texas Health Science Center at San Antonio (UTHSCSA), including: Professor, Department of Molecular Medicine/Institute of Biotechnology since 2007; Co-Leader, Cancer Development & Progression, Cancer Therapy & Research Center 2008; and Member, Executive Committee, Cancer Therapy & Research Center since 2009.

2. In 1985 I received a B.S. from Fudan University, Shanghai, PR China in genetics. In 1991 I received a Ph.D. from the University of California, Berkeley in molecular biology. From 1991 to 1993 I was a postdoctoral research fellow in DNA tumor viruses at the University of California, Berkeley. From 1994 to 1996 I was a postdoctoral research fellow in cell cycle control at Cold Spring Harbor Laboratories. I have served as both an assistant and an associate professor of biochemistry and molecular genetics at the University of Virginia. A copy of my *curriculum vitae* and a listing of my *BRCA1*-related publications are attached as Exhibits 1 & 2, respectively.

3. I began researching the *BRCA1* gene in 1999, shortly after Myriad's publication of the full-length *BRCA1* sequence. I have published 22 peer-reviewed articles reporting my research on the BRCA genes in research collaborations with over 50 different scientists around the world. I was aware that

aspects of the BRCA genes are covered by Myriad's patent rights.

4. During my research I have helped elucidate various physiological roles and properties of *BRCA1*. For example: [1]

(a) We discovered and/or further elucidated several aspects of *BRCA1* itself, including: BRCA1 alters the local chromatin structure and stimulates chromosomal DNA replication (which in turn suggests increasing chromatin accessibility may be an important mechanism used by other transcription factors to facilitate multiple nuclear processes) (ref. 22.); a new activation domain in BRCA1 that may contribute to the heterogeneous risk of BRCA1 mutations in different tissues. (ref. 20); BRCA1's role in processing the replication protein A-associated intermediates during double-stranded break repair (ref. 17); BRCA1's mechanisms for sensing xenobiotics and regulating AhR-dependent stress responses to these xenobiotics could play a role in BRCA1's tumor suppressing ability (ref. 3); and decreased BRCA1 confers tamoxifen resistance in breast cancer cells by altering estrogen receptor-coregulator interactions (ref. 1).

(b) We have helped in elucidating why BRCA1 deficiency leads disproportionately to breast and ovarian cancers. For example: BRCA1's coordinating role in gene expression may ensure the appropriate quantity and quality of the mature transcripts for certain breast and ovarian cancer-related genes, as well as the genetic integrity of the breast and ovary tissues (ref. 12); BRCA1 deficiency in epithelial and certain nonepithelial cells may result in combined effects of aberrant estrogen biosynthesis and compromised DNA repair capability, which in turn may lead to specific cancers in the breast and ovary (ref. 11); and in addition to its well-characterized activities in breast epithelial cells, a role of BRCA1 in modulation of estrogen biosynthesis in ASCs [adipose stromal cells] may also contribute to its tissue-specific tumor suppressor function (ref. 9).

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[1] "Ref._" below refers to the indicated publication listed in the attached Exhibit 2.

(c) We developed a novel chromatin unfolding assay that can aid in the characterization of deleterious mutations in the C-terminal transactivation domain of BRCA1 and may provide more reliable presymptomatic risk assessment. (Ref. 18.)

(d) We discovered and/or further elucidated the physiological relationship between BRCA1 and COBRA1. For example: A novel cofactor of BRCA1 (COBRA1) is recruited to the chromosome site by the first BRCT repeat of BRCA1, and is itself sufficient to induce chromatin unfolding (ref. 19); COBRA1 causes RNA polymerase II (RNAPII) to pause at the promoter-proximal region, which may be important to control the duration and magnitude of a rapid and reversible hormonal response (ref. 14); COBRA1 is a novel oncogene in upper gastrointestinal adenocarcinomas (ref. 10); COBRA1 plays a critical role in the regulation of clustered gene expression at preferred chromosomal domains in breast cancer cells (ref. 7); COBRA1 may coordinate multiple steps in ligand-dependent gene expression, which in turn ensures both the quantity and quality of hormone-stimulated gene products (ref. 6); COBRA1 and BRCA1, significant overlap of COBRA1- and BRCA1-regulated genes, may engage in common gene regulatory pathways to suppress breast cancer progression (ref. 5); and a lack of COBRA1 expression in breast carcinoma may serve as a useful indicator for poor prognosis (ref. 4).

5. This research involved, *inter alia*, plasmids containing *BRCA1* cDNA, heterologous cells expressing BRCA1 protein, primers designed to PCR amplify *BRCA1* cDNA, and antibodies against BRCA1 protein.

6. Until asked to prepare this declaration, I had never been contacted by Myriad Genetics, Inc. Neither the patents at issue in this suit nor Myriad Genetics have in any way hampered my research.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Rong Li
Rong Li, Ph.D

Executed on __12/08____, 2009

EXHIBIT 1

[EXHIBIT 1 OMITTED]

EXHIBIT 2

BRCA-SPECIFIC PUBLICATIONS BY DR. RONG LI

2. Wen J, Li R, Lu Y, Shupnik MA. Oncogene. 2009 Jan 29;28(4):575-86. Epub 2008 Nov 10. Decreased BRCA1 confers tamoxifen resistance in breast cancer cells by altering estrogen receptor-coregulator interactions.

3. Amleh A, Nair SJ, Sun J, Sutherland A, Hasty P, Li R. PLoS One. 2009;4(4):e5034. Epub 2009 Apr 2. Mouse cofactor of BRCA1 (Cobra1) is required for early embryogenesis.

4. Kang HJ, Kim HJ, Cho CH, Hu Y, Li R, Bae I. Cancer Chemother Pharmacol. 2008 Nov;62(6):965-75. Epub 2008 Feb 8. BRCA1 transcriptional activity is enhanced by interactions between its AD1 domain and AhR.

5. Sun J, Watkins G, Blair AL, Moskaluk C, Ghosh S, Jiang WG, Li R. J Cell Biochem. 2008 Apr 15;103(6):1798-807. Deregulation of cofactor of BRCA1 expression in breast cancer cells.

6. Aiyar SE, Cho H, Lee J, Li R. Int J Biol Sci. 2007 Nov 26;3(7):486-92. Concerted transcriptional regulation by BRCA1 and COBRA1 in breast cancer cells.

7. Sun J, Blair AL, Aiyar SE, Li R. J Steroid Biochem Mol Biol. 2007 Nov-Dec;107(3-5):131- 9. Epub 2007 Jun 27. Cofactor of BRCA1 modulates androgen-dependent transcription and alternative splicing.

8. Aiyar SE, Blair AL, Hopkinson DA, Bekiranov S, Li R. Oncogene. 2007 Apr 19;26(18):2543-53. Epub 2006 Oct 16. Regulation of clustered gene expression by cofactor of BRCA1 (COBRA1) in breast cancer cells.

9. Lu Y, Amleh A, Sun J, Jin X, McCullough SD, Baer R, Ren D, Li R, Hu Y. Mol Endocrinol. 2007 Mar;21(3):651-63. Epub 2006 Dec 21. Ubiquitination and proteasome-mediated degradation of BRCA1 and BARD1 during steroidogenesis in human ovarian granulosa cells.

10. Ghosh S, Lu Y, Katz A, Hu Y, Li R. Am J Physiol Endocrinol Metab. 2007 Jan;292(1):E246-52. Epub 2006 Aug 29. Tumor suppressor BRCA1 inhibits a breast cancer-associated promoter of the aromatase gene (CYP19) in human adipose stromal cells.

11. McChesney PA, Aiyar SE, Lee OJ, Zaika A, Moskaluk C, Li R, El-Rifai W. Cancer Res. 2006 Feb 1;66(3):1346-53. Cofactor of BRCA1: a novel transcription factor regulator in upper gastrointestinal adenocarcinomas.

12. Hu Y, Ghosh S, Amleh A, Yue W, Lu Y, Katz A, Li R. Oncogene. 2005 Dec 15;24(56):8343-8. Modulation of aromatase expression by BRCA1: a possible link to tissue-specific tumor suppression.

13. Aiyar S, Sun JL, Li R. J Cell Biochem. 2005 Apr 15;94(6):1103-11. Review. BRCA1: a locus-specific "liaison" in gene expression and genetic integrity.

14. Yordy JS, Moussa O, Pei H, Chaussabel D, Li R, Watson DK. Oncogene. 2005 Jan 27;24(5):916-31.

SP100 inhibits ETS1 activity in primary endothelial cells.

15. Aiyar SE, Sun JL, Blair AL, Moskaluk CA, Lu YZ, Ye QN, Yamaguchi Y, Mukherjee A, Ren DM, Handa H, Li R. Genes Dev. 2004 Sep 1;18(17):2134-46. Attenuation of estrogen receptor alpha-mediated transcription through estrogen-stimulated recruitment of a negative elongation factor.

16. Ye QN, Hu YF, Zhong HJ, Li R, Huang CF. Sheng Wu Gong Cheng Xue Bao. 2002 Nov;18(6):656-61. Chinese.. [Mapping of BRCT1 domain of BRCA1 with chromatin unfolding activity].

17. Hu YF, Li R. Genes Dev. 2002 Jun 15;16(12):1509-17. JunB potentiates function of BRCA1 activation domain 1 (AD1) through a coiled-coil-mediated interaction.

18. Choudhary SK, Li R. J Cell Biochem. 2002;84(4):666-74. BRCA1 modulates ionizing radiation-induced nuclear focus formation by the replication protein A p34 subunit.

19. Ye QN, Hu YF, Zhong HJ, Li R, Huang CF Yi Chuan Xue Bao. 2002;29(11):941-8. Chinese. [Studies of mutations in BRCA1 transactivation domain by visualization of chromatin structure].

20. Ye Q, Hu YF, Zhong H, Nye AC, Belmont AS, Li R. J Cell Biol. 2001 Dec 10;155(6):911-21. Epub 2001 Dec 10. BRCA1-induced large-scale chromatin unfolding and allele-specific effects of cancer-predisposing mutations.

21. Hu YF, Miyake T, Ye Q, Li R. J Biol Chem. 2000 Dec 29;275(52):40910-5. Characterization of a novel trans-activation domain of BRCA1 that

functions in concert with the BRCA1 C-terminal (BRCT) domain.

22. Miyake T, Hu YF, Yu DS, Li R. J Biol Chem. 2000 Dec 22;275(51):40169-73. A functional comparison of BRCA1 C-terminal domains in transcription activation and chromatin remodeling.

23. Hu YF, Hao ZL, Li R. Genes Dev. 1999 Mar 15;13(6):637-42. Chromatin remodeling and activation of chromosomal DNA replication by an acidic transcriptional activation domain from BRCA1.

[Declaration of Jeffrey Parvin, filed December 23, 2011] [Caption Omitted In Printing] [Exhibit 1 omitted]

I, Jeffrey D. Parvin, declare under penalty of perjury:

1. I currently hold several positions at The Ohio State University, including: Interim-Chair, Department of Biomedical Informatics since 2008; Director, Biomedical Informatics Shared Resource of the Ohio State University Comprehensive Cancer Center; Professor, Department of Biomedical Informatics since 2007; Louis Levy Professor for Cancer since 2007; and Adjunct Professor, Department of Molecular Virology, Immunology and Medical Genetics since 2008.

2. In 1982 I received a B.S. from Haverford College in chemistry. In 1987 I received a Ph.D. from the Mount Sinai School of Medicine in microbiology. In 1989 I received an M.D. also from Mount Sinai School of Medicine. From 1989-1994 I was a postdoctoral research fellow in biology at the Center for Cancer Research at Massachusetts Institute of Technology. I have served as both an assistant and an associate professor of pathology at the Harvard Medical School. A copy of my *curriculum vitae* and a listing of my *BRCA1*-related publications are attached as Exhibits 1 & 2, respectively.

3. I began researching the *BRCA1* gene in 1997, shortly after Myriad's publication of the full-length *BRCA1* sequence. I have published 21 peer-reviewed articles reporting my research on the BRCA genes in research collaborations with over 80 different scientists around the world. My most current

BRCA1 research has yielded another paper in press to be published in early 2010 and yet another awaiting review. I have also published 12 articles reviewing the BRCA research conducted by others. I was aware that Myriad patents cover aspects of the BRCA genes.

4. During my *BRCA1* research I have helped elucidate various physiological roles and properties of the protein encoded by the *BRCA1* gene. For example:[2]

(a) BRCA1 plays a role in DNA damage repair and the cell cycle (*e.g.*, BRCA1 and BARD1 heterodimerization is stabilized via domains not previously thought to interact and BARD1 acts in both ubiquitination-dependent and ubiquitination-independent ways to influence the role of BRCA1 in DNA repair). (Refs. 21 & 23.)

(b) BRCA1 is an RNA polymerase II holoenzyme-bound protein involved in both transcription activation and repression (e.g., the BRCA1 domain responsible for transcription regulation). (Refs. 1, 4, 7, 16, & 17.)

(c) Defective BRCA1 plays a role in cancer genesis via disregulated centrosome duplication, including the specific ubiquitination domains involved in such disregulation. (Refs. 13, 14, 18, 19, & 20.)

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[2] "Ref. _" below refers to the indicated publication listed in the attached Exhibit 2.

(d) Multiple distinct protein complexes comprising BRCA1 mediate the multiple processes with which BRCA1 is involved (rather than one supercomplex). (Ref. 6.)

(e) BRCA1 is involved in histone modification. (Ref. 22.)

(f) Despite previous focus on BRCA1's conserved amino- and carboxy termini, an internal ubiquitin ligase domain of BRCA1 mediates a potent growth suppressive effect. (Ref. 9.)

(g) My *BRCA1* research has even helped elucidate the functions of other transcription activation proteins based on their interaction with BRCA1 protein. (Ref. 5.)

5. This research involved, *inter alia*, plasmids containing *BRCA1* cDNA, heterologous cells expressing BRCA1 protein, primers designed to PCR amplify *BRCA1* cDNA, and antibodies against BRCA1 protein.

6. Until asked to prepare this declaration, I had never been contacted by Myriad Genetics, Inc. Neither the patents at issue in this suit nor Myriad Genetics, Inc., have in any way hampered my research.

I declare, pursuant to 28 U.S.C. §1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Jeffrey D. Parvin

Jeffrey D. Parvin, MD, Ph.D

Executed on 12/08, 2009

EXHIBIT 1

[EXHIBIT 1 OMITTED]

EXHIBIT 2

BRCA1 specific papers by Dr. Jeffrey Parvin

Original Research

1. Scully R, Anderson SF, Chao DM, Wei W, Ye L, Young RA, Livingston DM, **Parvin JD**. BRCA1 is a component of the RNA polymerase II holoenzyme. **Proc Natl Acad Sci USA** 1997; 94: 5605-10.

2. Neish AS, Anderson SF, Schlegel BP, Wei W, **Parvin JD**. Factors associated with the mammalian RNA polymerase II holoenzyme complex. **Nuc Acids Res** 1998; 26: 847-53.

3. Anderson SF, Schlegel BP, Nakajima T, Wolpin ES, **Parvin JD**. BRCA1 protein is linked to the RNA polymerase II holoenzyme complex via RNA helicase A. **Nature Genetics** 1998; 19: 254-6.

4. Haile DT, **Parvin JD**. Activation of transcription *in vitro* by the BRCA1 carboxy-terminal domain. **J Biol Chem** 1999; 274, 2113-7.

5. Schlegel BP, Green VJ, Ladias JAA, **Parvin JD**. BRCA1 interaction with RNA polymerase II reveals a role for hRPB2 and 10α in activated transcription. **Proc Natl Acad Sci USA** 2000; 97, 3148-53.

6. Chiba N, **Parvin JD** Redistribution of BRCA1 among four different protein complexes following replication blockage. **J Biol Chem** 2001; *276*, 38549-54.

7. Chiba N, **Parvin JD**. The BRCA1 and BARD1 association with the RNA polymerase II holoenzyme. **Cancer Research** 2002; *62*, 4222-8.

8. Schlegel BP, Starita LM, **Parvin JD**. Overexpression of a protein fragment of RNA Helicase A causes inhibition of endogenous BRCA1 function and defects in ploidy and cytokinesis in mammary epithelial cells. **Oncogene** 2003; *22*, 983-91.

9. You F, Chiba N, Ishioka C, and **Parvin JD**. Expression of an amino-terminal BRCA1 deletion mutant causes a dominant growth inhibition in MCF10A cells. **Oncogene** 2004; *23*, 5792-5798.

10. Starita LM, Machida Y, Sankaran S, Elias JE, Griffin K, Schlegel BP, Gygi SP, and **Parvin JD**. BRCA1-dependent ubiquitination of γ-tubulin regulates centrosome number. **Mol Cell Biol.** 2004; *24*, 8457-8466.

11. Starita LM, Horwitz AA, Keogh MC, Ishioka C, **Parvin JD***, and Chiba N*. BRCA1/BARD1 ubiquitinate phosphorylated RNA polymerase II. **J Biol Chem** 2005; *280*, 24498-505. (*co-corresponding authors)

12. Sankaran S, Starita LM, Groen AC, Ko MJ, and **Parvin JD**. Centrosomal microtubule nucleation activity is inhibited by BRCA1-dependent ubiquitination. **Mol Cell Biol.** 2005; *25*, 8656-68.

13. Ko MJ, Murata K, Hwang DS, and **Parvin JD**. Inhibition of BRCA1 in breast cell lines causes the centrosome duplication cycle to be disconnected from the cell cycle. **Oncogene** 2006; *25*, 298-303.

14. Simons, AM, Horwitz, AA, Starita, LM, Williams, RS, Griffin, K, Glover, JNM, and **Parvin, JD**. BRCA1 DNA binding activity is stimulated by BARD1. **Cancer Res** 2006; *66*, 2012-8.

15. Sankaran, S, Starita, LM, Simons, AM, and **Parvin, JD**. Identification of domains of BRCA1 critical for the ubiquitin-dependent inhibition of centrosome function. **Cancer Res** 2006: *66*, 4100-7.

16. Horwitz AA, Sankaran S, and **Parvin JD**. Direct stimulation of transcription initiation by BRCA1 requires both its amino and carboxy-termini. **J Biol Chem** 2006 *281*, 8317-20. (accelerated publication)

17. Horwitz AA, Affar EB, Heine GF, Shi Y, and **Parvin JD**. A mechanism for transcriptional repression dependent on the BRCA1 E3 ubiquitin ligase. **Proc Natl Acad Sci USA** 2007 *104*, 6614-9.

18. Pujana, MA*, Han, JD*, Starita, LM*, Stevens, Kn*, Tewari, M, Ahn, JS, Rennert, G; Moreno, V, Assmann, V, ElShamy, WM, J Rual, JF, Rozek, LS, Gelman, RS, Gunsalus, KC, Greenberg, RA, Sobhian, B, Bertin, N, Venkatesan, K, Ayivi-Guedehoussou, N, Lázaro, C, Nathanson, KL, Weber, BL, Cusick, ME, Hill, DE, Livingston, DM, Gruber, SB**, **Parvin, JD****, and Vidal, M**. Network modeling links breast cancer susceptibility and centrosome dysfunction. **Nat Genet** 2007 *39*, 1338-49. (*co-first authors; **co-corresponding authors)

19. Sankaran S, Crone DE, Palazzo RE, and **Parvin JD**. Aurora A Kinase Regulates BRCA1 Inhibition of Centrosome-Dependent Microtubule Nucleation. **Cancer Res** 2007 *67*, 11186-94.

20. Sankaran S, Crone DE, Palazzo RE, and **Parvin JD**. BRCA1 regulates γ-tubulin binding to centrosomes. **Cancer Biology and Therapy** 2007 *6*: 1853-7.

21. Johnson N, Cai D, Kennedy RD, Pathania S, Arora M, D'Andrea AD, **Parvin JD**, and Shapiro GI. CDK1 participates in BRCA1-dependent S phase checkpoint control in response to DNA damage. **Mol Cell** 2009 *35*:327-39.

22. Thakar A, **Parvin JD**, Zlatanova J. BRCA1/BARD1 E3 ubiquitin ligase can modify histones H2A and H2B in the nucleosome particle. **Journal of Biomolecular Structure & Dynamics** 2010 *27 In press*

23. *Ransburgh DJR, *ChibaN, Ishioka C, Toland AE, and **Parvin JD**. The effect of BRCA1 missense mutations on homology directed recombination. *Submitted*.

Reviews

1. **Parvin JD**, Young RA. Regulatory targets in the RNA polymerase II holoenzyme. **Current Opinion in Gen & Dev** 1998; 8: 565-70.

2. Mondal N, **Parvin JD**. BRCA1 function in transcription. Gene Therapy and Molecular Biology, 1999; 4: 397-404.

3. **Parvin JD**. BRCA1 at a branch point. **Proc Natl Acad Sci USA** 2001; *98*, 5952-4.

4. **Parvin JD**. Creating a tool-kit for exploring BRCA1 function. **Cancer Biology and Therapy** 2002; *1*, 509-10.

5. Starita LM, **Parvin JD**. The multiple nuclear functions of BRCA1: transcription, ubiquitination, and DNA repair. **Current Opinion In Cell Biology** 2003; *15*, 345-50.

6. **Parvin JD**. Overview of History and Progress in BRCA1 Research: The First BRCA1 decade. **Cancer Biology and Therapy** 2004; *3*, 505-8.

7. Starita LM, **Parvin JD**. Substrates of the BRCA1 dependent ubiquitin ligase. **Cancer Biology and Therapy** 2006; *5*, 137-41.

8. **Parvin JD**, Sankaran S. The BRCA1 E3 ubiquitin ligase controls centrosome dynamics. **Cell Cycle** 2006; *5*, 1946-50.

9. Sankaran S, **Parvin JD**. Centrosome function in normal and tumor cells. **J Cell Biochem** 2006; *99*,1240-50.

10. Heine GF, **Parvin JD**. BRCA1 Control of Steroid Receptor Ubiquitination. **Science STKE** 2007; *391*, pe34.

11. Kais Z, **Parvin JD**. Regulation of centrosomes by the BRCA1-dependent ubiquitin ligase. **Cancer Biology and Therapy** 2008; *7*, 1540-3.

12. **Parvin JD**. The BRCA1-dependent ubiquitin ligase, γ-tubulin, and centrosomes. **Environmental and Molecular Mutagenesis**, 2009; *50*: 649-53.

[Declaration of Gregory Critchfield, filed December 23, 2009] [Caption Omitted In Printing] [Exhibits 1-6 omitted]

I, Gregory C. Critchfield, declare:

1. I am President of Myriad Genetic Laboratories, Inc., a wholly owned subsidiary of Myriad Genetics, Inc. (referred together as "Myriad"). I have held this position since July 1998. I received my M.D. from the University of Utah, and my M.S. in Biophysical Sciences from the University of Minnesota. I am Board Certified in Clinical Pathology. Before joining Myriad, I served as Senior Vice President, Chief Medical and Science Officer of Quest Diagnostics Inc. A copy of my curriculum vitae and a list of publications by me are provided in the **Exhibits 1 and 2**, respectively.

I. MYRIAD'S PATENT RIGHTS HAVE PROMOTED RESEARCH

2. Myriad was founded to conduct innovative research to discover and isolate disease genes, and to commercialize genetic testing based on the disease genes. Today Myriad is still active in research and discovery to develop prognostic, personalized, and predictive medicine testing products. It is in Myriad's own interest that neither basic nor clinical research be stifled by patents. In fact, Myriad has consistently promoted and encouraged both basic and clinical research on the *BRCA1* and *BRCA2* genes by others, by (1) allowing academic scientists to conduct research studies on the *BRCA1* and *BRCA2* genes freely; (2) providing direct assistance to researchers in their studies on the *BRCA1* and *BRCA2* genes; and (3) conducting its own research on the *BRCA1*

and *BRCA2* genes, publishing the research results and actively disseminating information on the *BRCA1* and *BRCA2* genes.

Myriad Allows Research on the *BRCA1* and *BRCA2* Genes Freely

3. It has been, and still is, Myriad's policy and practice to allow scientists to conduct research studies on the *BRCA1* and *BRCA2* genes freely. This has been commonly understood by academic scientists in the field. For example, Plaintiff Wendy Chung acknowledges that researchers "could sequence the *BRCA1* and *BRCA2* genes for purely research purposes." D. Chung ¶ 15. In fact, Dr. Chung has been doing so. *See e.g.*, D. Chung ¶ 11 ("As part of my molecular genetics research, we sequence human genes, including the *BRCA1* and *BRCA2* genes of research subjects in my research lab. We look at the sequences to determine if there are any alterations and investigate whether those alterations have clinical significance."). Indeed, tens of thousands of researchers have been conducting research on the *BRCA1* and *BRCA2* genes and published thousands of research papers on the *BRCA1* and *BRCA2* genes. *See* ¶ 13 below; *see also*, D. Parvin; D. Li; D. Baer; D. Sandbach.

Myriad Provides Direct Assistance to Researchers in Their Studies

4. Myriad and its collaborators published their landmark research on the *BRCA1* and *BRCA2* genes in 1994 and 1996, respectively. Since then, Myriad has provided assistance to researchers around the world in their independent studies on the genes.

5. Since 1994, Myriad has provided genetic materials such as cDNA clones of the *BRCA1* and *BRCA2* genes free to researchers at over 30 research institutions all over the world, including, among others, the University of Pennsylvania, Emory University, the University of Chicago, and the University of Rochester. These researchers have since published a total of 336 peer-reviewed scientific papers related to *BRCA1* and *BRCA2*.

6. Myriad also has a policy to collaborate with researchers on studies relating to the *BRCA1* and *BRCA2* genes. In fact, since the *BRCA1* and *BRCA2* genes were discovered, Myriad has collaborated with over 440 outside researchers and participated in more than 110 research programs/studies by outside researchers in further studies of *BRCA 1* and *BRCA2*.

7. For example, in 1999, to further encourage research on the *BRCA1* and *BRCA2* genes, I proposed to Dr. Richard Klausner, the then National Cancer Institute ("NCI") Director, for Myriad to provide *BRCA* testing services to researchers conducting studies funded by NCI and other NIH Institutes. In December 1999, a Memorandum of Understanding (MOU) between Myriad and NCI was signed. Under the MOU, Myriad agreed to provide research testing services at a fraction of the commercial testing price to researchers conducting research funded by NCI or another Institute under the National Institute of Health. The MOU was renewed twice for a total of six years. During those six years, 178 scientists received the discounted research testing services and 5,932 individuals were tested for *BRCA* mutations under the MOU. This

program provided support for a number of key research groups that led to important publications on *BRCA* mutation prevalence and the value of clinical intervention in *BRCA* mutation carriers.

8. In another important area, Myriad worked with noted researchers on efforts to classify genetic variants of uncertain clinical significance ("VUS"), making data available from our large sequence database.[3] In these studies, Myriad provided the researchers with information from its database of gene sequence information built upon the largest scale of clinical genetic testing on *BRCA1* and *BRCA2* in the world. This was critical to the researchers' studies. The published research results have the potential of improving the diagnostic testing for a number of other genes.

9. Myriad's contribution to research is also evidenced by the tens of millions of dollars in patent royalty payments made to research institutions such as the University of Utah, National Institute of Health, the University of Pennsylvania, the University of Toronto, and Laval University, all of which collaborated with Myriad in research to identify and isolate the *BRCA1* and *BRCA2* genes.

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[3] *See e.g.*, Abkevich *et al.*, *Analysis of Missense Variation in Human* BRCA1 *in the Context of Interspecific Sequence Variation*, J. MED. GENET., 40:492-507 (2004); Goldgar *et al.* & Breast Cancer Information Core (BIC) Steering Committee, *Integrated Evaluation of DNA Sequence Variants of Unknown Clinical Significance: Application to* BRCA1 *and* BRCA2, AM. J. MED. GENET., 75:535-544 (2004).

Myriad Actively Publishes Its Own Research and Disseminates Scientific Information on the *BRCA1* and *BRCA2* Genes

10. Besides assisting outside researchers in their research, Myriad also has been actively conducting its own research for a better understanding of the *BRCA1* and *BRCA2* genes. More importantly, Myriad has been actively publishing its research findings in peer-reviewed journals, and abstracts and posters in scientific meetings. To date, Myriad has made 128 publications on the *BRCA1* and *BRCA2* genes in peer-reviewed journals and scientific meetings.

11. Shortly after the discoveries of the *BRCA* genes by Myriad and its collaborators, Myriad, under no obligation to do so, worked with other researchers to build the Breast Cancer Information Core ("BIC") database (http://www.research.nhgri.nih.gov/bic/), a central repository for information regarding *BRCA* mutations. The BIC database is an open access on-line database that provides valuable information to scientists in their early research on the *BRCA1* and *BRCA2* genes. Myriad is the largest contributor to this database, and made more than 20,000 submissions to the database.

12. In addition, Myriad has published the most clinical data on mutation risk in the *BRCA1* and *BRCA2* genes based on its extensive experience from the largest scale of genetic testing ever conducted in

the world.[4] The mutation risk data have been tabulated and posted on Myriad's website (http://www.myriadtests.com/provider/mutprevo.htm), and are frequently updated by Myriad and freely available to researchers and clinicians throughout the world. Using these mutation prevalence tables, researchers and physicians can readily determine an individual's predicted risk of harboring a deleterious *BRCA* mutation based on his or her personal cancer history and family history. *See* Exhibit 3. These tables have been widely accessed by researchers and clinicians worldwide.

Significant Progress Has Been Made in Research on the *BRCA* Genes

13. Scientific research in *BRCA*-associated hereditary breast and ovarian cancers not only has been made possible by the landmark discoveries and publications by Myriad and its collaborators, but also has been significantly promoted by Myriad's policy and practice as summarized above. Indeed, a recent search of the PubMed medical literature database shows that since Myriad's publications of the discoveries of the *BRCA1* and *BRCA2* genes in October, 1994,[5] and March 1996,[6] respectively, more

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[4] *See* Frank *et al.*, *Clinical Characteristics of Individuals with Germline Mutations in* BRCA1 *and* BRCA2: *Analysis of 10,000 Individuals*, J. CLIN. ONCOL., 20:1480-90 (2002).

[5] Miki *et al.*, *A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene* BRCA1, SCIENCE, 266:66-71 (1994).

[6] Tavtigian *et al.*, *The Complete* BRCA2 *Gene and Mutations in Chromosome 13q-Linked Kindreds*, NAT. GENET., 12:333-7 (1996).

than 18,000 scientists have researched the *BRCA* genes, publishing more than 5,600 research papers on *BRCA1* and over 3,000 research papers on *BRCA2*. Many of these scientists are members of the institutional Plaintiffs in this suit including the Association for Molecular Pathology, American College of Medical Genetics, American Society for Clinical Pathology, and College of American Pathologists. Among these scientists are also members of *amici* supporting the Plaintiffs' case including the American Medical Association, American Society of Human Genetics, American College of Obstetricians and Gynecologists, American College of Embryology, and the Medical Society of the State of New York. Notably, the individual plaintiffs in this suit and their supporting declarants alone have published a total of 48 peer-reviewed research papers on the *BRCA1* and *BRCA2* genes. *See* Exhibit 4.

14. Thanks in part to Myriad's active effort in promoting research, scientists have made impressive progress in understanding and even harnessing the *BRCA1* and *BRCA2* genes. For example, when Myriad and its collaborators identified and isolated the *BRCA1* and *BRCA2* genes, the data showing their association with predisposition to cancer was generated from selected Caucasian family pedigrees. Researchers now know that mutations in the *BRCA1* and *BRCA2* genes confer high risk for hereditary breast and ovarian cancer in a variety of human

population groups.[7] Also, when the genes were discovered, the biological mechanism underlying their association with cancer was unknown. Today, scientists understand that functional BRCA1 and BRCA2 proteins prevent mutations and cancer through homologous recombination by repairing double-stranded DNA damages.[8]

15. Importantly, extensive clinical research has uncovered various means to reduce the risk of breast and ovarian cancer once *BRCA* mutations carriers are identified. For example, the risk of breast cancer can be reduced by up to 90% by prophylactic mastectomy in *BRCA* mutation carriers.[9] The risk of breast cancer can be reduced as much as 72% by prophylactic oophorectomy in *BRCA* mutation carriers.[10] The risk for ovarian cancer is reduced by 85-96% by prophylactic risk- reducing oophorectomy

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[7] *See* James D. Fackenthal & Olufunmilayo I. Olopade, *Breast Cancer Risk Associated with* BRCA1 *and* BRCA2 *in Diverse Populations*, NAT. REV. CANCER, 7:937-948 (2007).

[8] *See e.g.*, Gowen *et al.*, BRCA1 *Required for Transcription-Coupled Repair of Oxidative DNA Damage*, SCIENCE, 281:1009-12 (1998); Welcsh *et al.*, *Insights into the functions of* BRCA1 *and* BRCA2, TRENDS GENET., 16:69-74 (2000).

[9] *See e.g.*, Hartmann *et al.*, *Efficacy of Bilateral Prophylactic Mastectomy in* BRCA1 *and* BRCA2 *Gene Mutation Carriers*, J. NATL. CANCER INST., 93:1633-7 (2001); Rebbeck *et al.*, *Bilateral Prophylactic Mastectomy Reduces Breast Cancer Risk in* BRCA1 *and* BRCA2 *Mutation Carriers: the PROSE Study Group*, J. CLIN. ONCOL., 22:1055-62 (2004).

[10] *See e.g.*, Kauff *et al.*, *Risk-Reducing Salpingo-Oophorectomy for the Prevention of* BRCA1- *and* BRCA2-*Associated Breast and Gynecologic Cancer: A Multicenter, Prospective Study*, J. CLIN. ONCOL., 26:1331-7 (2008).

in *BRCA* mutation carriers.[11] In addition, mortality risk can be significantly reduced by bilateral prophylactic risk-reducing salpingo-oophorectomy in *BRCA* mutation carriers.[12] Also, tamoxifen use in *BRCA* mutation carriers for five years reduces the odds of contralateral breast cancer by 50%.[13] Finally, researchers have also found that the use of oral contraceptives for at least six years is associated with a 60% decreased risk of ovarian cancer.[14]

16. Exciting research on the *BRCA* genes has also suggested improved and personalized chemotherapies in cancer patients. For example, scientists have found that breast cancer tumors must possess intact BRCA function in order to exhibit sensitivity to spindle poisons such as taxol and vinblastin, while tumors lacking BRCA function exhibit increased sensitivity to cytotoxic DNA-damaging agents such as cisplatin.[15]

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[11] *See e.g.*, Rebbeck *et al.*, *Prophylactic Oophorectomy in Carriers of* BRCA1 *or* BRCA2 *Mutations*, N. ENGL. J. MED., 346:1616-22 (2002).

[12] *See e.g.*, Domchek *et al.*, *Mortality after Bilateral Salpingo-Oophorectomy in* BRCA1 *and* BRCA2 *Mutation Carriers: A Prospective Cohort Study*, LANCET ONCOL., 7:223-9 (2006).

[13] *See e.g.*, Narod *et al.*, *Tamoxifen and Risk of Contralateral Breast Cancer in* BRCA1 *and* BRCA2 *Mutation Carriers: A Case-Control Study*, LANCET, 356:1876-1881 (2000).

[14] *See e.g.*, Narod *et al. Oral Contraceptives and the Risk of Hereditary Ovarian Cancer*, N. ENGL. J. MED., 339:424-428 (1998).

[15] *See e.g.*, Kennedy *et al.*, *The Role of* BRCA1 *in the Cellular Response to Chemotherapy*, J. NATL. CANCER INST., 96:1659-68 (2004); Farmer *et al.*, *Targeting the DNA Repair Defect in BRCA*

17. Indeed, new drugs such as PARP1 inhibitors are being developed targeting the biological pathway centering around BRCA1 and BRCA2 proteins in cancer cells. Examples of such PARP1 inhibitor drugs in development include olaparib (also known as AZD2281) by AstraZeneca[16], BSI-201 by BiPar Sciences Inc.[17], ABT-888 by Abbott Laboratories, Inc.[18], and AG014699 by Pfizer[19]. Screening for *BRCA1* and *BRCA2* mutations can allow such drugs to be administered specifically to cancer patients harboring such mutations. This personalized approach provides patients with optimized treatment while avoiding wasteful spending on ineffective therapies. As a matter of fact, Myriad has been using its expertise in *BRCA* mutation screening to

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Mutant Cells as A Therapeutic Strategy, NATURE, 434:917-21 (2005).

[16] Fong *et al.*, *Inhibition of Poly(ADP-ribose) Polymerase in Tumors from BRCA Mutation Carriers*, N. ENGL. J. MED., 361:123-34 (2009).

[17] Kopetz *et al.*, *First in Human Phase I Study Of BSI-201, A Small Molecule Inhibitor of Poly ADP-Ribose Polymerase (PARP) in Subjects with Advanced Solid Tumors*, J. CLIN. ONCOL., 26(suppl.) abstr. 3577 (2008).

[18] Yang *et al.*, *Immunohistochemical Detection of Poly(ADP-Ribose) Polymerase Inhibition by ABT-888 in Patients with Refractory Solid Tumors and Lymphomas*, CANCER BIOL. THER., 8:2002-7 (2009).

[19] Plummer *et al.*, *Phase I Study of the Poly(ADP-Ribose) Polymerase Inhibitor, AG014699, in Combination with Temozolomide in Patients with Advanced Solid Tumors*, CLIN. CANCER RES., 14:7917-23 (2008).

help AstraZeneca in its development of olaparib, which has shown great promise in clinical trials.

18. In summary, tremendous progress has been made in the field of *BRCA1* and *BRCA2* and hereditary breast and ovarian cancer. Because of all the research in this area, physicians today are able to conveniently estimate the risk of *BRCA* mutation in a given individual, and identify candidates for BRAC*Analysis*® testing. Moreover, once *BRCA* mutations are detected, effective options validated by research are available to reduce the risk of breast and ovarian cancer in healthy individuals or the risk of second cancer in cancer patients. In addition, tailored chemotherapy regimens can be selected for cancer patients based on the *BRCA* mutation status. More excitingly, effective PARP1 inhibitors targeting tumors with *BRCA* mutation are on the horizon. Myriad's discovery and publication of the *BRCA1* and *BRCA2* genes opened the doors to all of these advances in science. Myriad's policy and practice of promoting research has facilitated such significant progress in science and medicine. The notion advanced by the Plaintiffs that research has been stifled by the patents at issue in this lawsuit is contradicted by the evidence.

Myriad Has Never Stopped Scientists from Doing Research

19. In the late 1990s, Myriad sent cease and desist letters to the University of Pennsylvania regarding the commercial (not research) *BRCA* testing activities of Drs. Haig Kazazian and Arupa Ganguly at the Genetic Diagnostic Laboratory on the campus. The purpose of these letters was to request that Drs. Haig Kazazian and Arupa Ganguly cease their

commercial diagnostic testing. Myriad has never requested Drs. Kazazian and Ganguly, or anyone else, to not conduct research.

20. Plaintiffs Haig Kazazian and Arupa Ganguly at the Genetic Diagnostic Laboratory of the University of Pennsylvania were very quick in rushing to commercially exploit the fruits of the hard-earned discoveries by Myriad and its collaborators. The commercial nature of their *BRCA* testing services in the 1990s has been admitted by Plaintiff Kazazian. *See e.g.,* D. Ganguly ¶ 4; D. Kazazian, ¶¶ 3, 4, 8 and 10 ("At the time we were forced to stop offering BRCA genetic services, we were charging patients less than Myriad was charging.") (emphasis added). As Dr. Kazazian stated, "[t]hrough the Genetic Diagnostic Laboratory, Dr. Ganguly and I provide state-of-the-art DNA-based diagnostic testing for a variety of genetic conditions and diseases, as well as prenatal and predictive testing and genetic counseling services." D. Kazazian, ¶ 3 (emphasis added). The commercial nature of the lab is also confirmed by the information on its website.[20] For example, billing (CPT) codes are associated with every genetic test the lab offers. For any testing by their lab, "[p]ayment is required with sample submission. Patients may choose to pay for their testing on a major credit card or submit a money order or personal check payable to the Genetic Diagnostic Laboratory. *See id.; see also* Exhibit 5.

21. The *BRCA* testing by Dr. Ganguly offered to the Cancer Genetics Network Project in 1998-1999

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[20] *See* Penn Medicine: The Genetic Diagnostic Laboratory, http://www.med.upenn.edu/gdl/ (last visited December 8, 2009).

was also commercial in nature. D. Ganguly ¶ 12, 13. The principal involvement by Dr. Ganguly in the Project was conducting DNA testing on the *BRCA1* and *BRCA2* genes for fees. *See id.* Dr. Ganguly's lab was acting as a central core lab for researchers much like other commercial core labs. In a meeting in late 1999 at the National Cancer Institute ("NCI") with Dr. Kazazian and Dr. Richard Klausner, the then NCI director, Dr. Klausner clearly told Dr. Kazazian that the *BRCA* testing Drs. Kazazian and Ganguly were conducting was clearly commercial and did not qualify as research.

22. Moreover, during a personal meeting with Plaintiff Dr. Haig Kazazian sometime between 1999 and 2000, I told him that he was free to do academic research on the *BRCA1* and *BRCA2* genes including sequencing the genes and detecting mutations in the genes.

23. There is simply no evidence that Myriad has stopped or deterred any scientists from conducting research.

II. PATENTS HAVE PROMOTED PATIENT ACCESS TO *BRCA* TESTING

24. I believe broad "patient access" to a genetic test requires that (1) there be significant awareness and understanding of the test by patients and their healthcare providers, and as a result, there is a desire for the test by those patients who may benefit from the test, (2) the test be of high quality and readily available when patients need it and test results are obtained in a timely manner, and (3) the test be affordable to most patients.

25. To date, Myriad has performed over 400,000 BRAC*Analysis*® tests for *BRCA* mutations. We receive tests from all 50 states. Over 40,000 healthcare providers have ordered and used the test. Presently, test results are typically available within two weeks. More than 90% of the BRAC*Analysis*® tests ordered by healthcare providers are covered by insurance, and the average reimbursement rate is over 90% of the cost of the test. There are more than 2,600 insurance payors who reimburse for the BRAC*Analysis* ® test. There are more than 80,000 insurance plans that cover the BRAC*Analysis* ® test. This undeniable "patient access" is the very result of Myriad's enormous investment in research, development, insurance coverage, and more importantly in raising patient and physician awareness and understanding of the test. Myriad would not have made the investment of more than 200 million dollars in raising patient and physician awareness alone without the protection provided by the exact patents the Plaintiffs are challenging. Myriad's story stands as a clear example of societal benefit due to patent protection. I am not aware of any diagnostic or pharmaceutical company that has made, or would be willing to make, this enormous investment without the benefit of a limited period of exclusivity engendered by patent rights.

The Awareness Barrier

26. When Myriad launched the commercial BRAC*Analysis*® test in late 1990s to screen for mutations in the *BRCA1* and *BRCA2* genes, knowledge about the genes was largely limited to genetic researchers in universities. Moreover, the greatest benefit of the test is to find healthy carriers

of *BRCA* mutations who have not developed cancer, so that early surveillance and preventive measures can be offered to these individuals. Without a good understanding of the role that *BRCA* mutations play in hereditary breast and ovarian cancer and genetic testing, there is little motivation for healthy individuals to even seek advice on genetic testing or their risks for predisposition to hereditary cancer.

27. To bring genetic testing, or the BRAC*Analysis*® test, to those patients who can benefit from it, Myriad had to invest significant time and money to raise the awareness and understanding of genetic testing to patients and their healthcare providers, and to educate and convince the insurance industry of the pharmacoeconomics of the test. For example, Myriad has established a 300-person sales force calling on oncologists and OBGYN doctors all over the country. Our sales representatives, genetic counselors and medical specialists are well-trained and well-versed on our tests. They meet personally with physicians, nurses and genetic counselors, providing them with research papers and educational materials, answering questions on our tests, and helping in testing logistics. Our large team of in-house genetic counselors and medical experts provide their expertise to help healthcare providers understand *BRCA* mutations, the BRAC*Analysis*® test and hereditary breast and ovarian cancer. In addition, Myriad organizes hundreds of educational meetings for physicians to learn about *BRCA* testing and hereditary breast and ovarian cancer from thought leaders who share their experience with their peers ("speakers programs"). For example, during the July – September, 2009 quarter alone, Myriad organized

more than 300 such speakers programs all over the country.

28. Direct proactive approaches in patient education have been shown in research studies to be especially important in getting the message across to healthy family members of cancer patients about the benefit of undergoing *BRCA* mutation screening.[21] Significantly, we have invested millions of dollars in patient awareness promotions on TV and other popular media to raise the awareness of hereditary breast and ovarian cancer and BRAC*Analysis*® testing. Such promotions introduce hereditary breast and ovarian cancer and encourage people who may be at risk for hereditary cancer to speak to their healthcare providers about their personal and family history of cancer to determine if genetic testing is appropriate for them. Our patient and physician outreach has made the BRAC*Analysis*® test available even in more remote rural areas. Without patent exclusivity, Myriad would not have made these investments.

29. Indeed, because of Myriad's efforts, we now routinely receive patient samples from everywhere in all 50 states. More than 40,000 physicians and genetic counselors have used the BRAC*Analysis*®

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[21] *See e.g.*, Evans *et al.*, *Comparison of Proactive and Usual Approaches to Offering Predictive Testing for* BRCA1/2 *Mutations in Unaffected Relatives*, CLIN. GENET., 75:124-32 (2009); *see also* Suthers *et al.*, *Letting the Family Know: Balancing Ethics and Effectiveness When Notifying Relatives about Genetic Testing for A Family Disorder*, J. MED. GENET., 43:665-670 (2006).

test. Over 400,000 patients who meet testing criteria have been tested at Myriad for mutations in the *BRCA1* and *BRCA2* genes. To say that Myriad's patent rights have limited patient access is simply ignoring the facts. To the contrary, patient awareness and access to important genetic testing has been significantly enhanced as a result of the patent grants at issue in this case.

30. The diagnostic labs run by the geneticists plaintiffs such as those by Drs. Kazazian and Ganguly (the Genetic Diagnostic Laboratory at the University of Pennsylvania), Dr. Harry Ostrer (the Genetic Lab at NYU Langone Medical Center) and Drs. David Ledbetter and Stephen Warren (at Emory Genetics Laboratory) are all within major universities typically serving only patients within the major teaching hospitals affiliated with their respective universities. None of them would have been able to make the substantial capital investment to do what Myriad has done in raising awareness and understanding of *BRCA* testing and reaching individuals who need these test services most, even in rural communities.

The Cost Barrier

31. Insurance reimbursement is a major barrier for patient access to any medical product. Myriad has invested significantly in building a strong marketing department including a team of experts specialized in working with insurance payors (private insurance companies, state-run Medicaids and Medicare) for reimbursement agreements to cover the cost of genetic testing. Today, Myriad has in place over 400 contracts with private insurance payors that cover over 130 million lives in the US.

Additional lives are covered under Medicaid and Medicare plans. In fact, between July 2007 and now, more than 2,600 insurance payors have reimbursed the BRAC*Analysis*® test under more than 80,000 insurance plans.

32. To reduce the out-of-pocket expense for patients, Myriad has set up a large Billing and Customer Service Department. Almost 150 individuals in this department interact daily with patients, their doctors, and their insurance companies to help patients work through the complexities of insurance coverage that could potentially prevent patients from receiving important testing services. Due to their efforts, over 90% of the tests Myriad performs are covered by insurance at over 90% of the test cost. As a result, for the 90% of testing covered by insurance, the weighted average out-of-pocket cost to each patient is less than $100.

33. At Myriad, we also understand that there are patients in our country who do not have insurance and need help. Since 1996 when BRAC*Analysis*® was launched, Myriad has had a financial assistance program directly providing free testing to low-income, uninsured patients. Just in the last four years, more than 3,000 patients have received free *BRCA* testing under this program (about 55 tests a month). In addition, Myriad also makes free testing available to needy patients through independent non-profit organizations such as the Cancer Resource Foundation ("CRF") in Massachusetts. *See* http://www.breastcancerma.org/helping-hand/#genetic. In fact, through the CRF,

MassHealth patients such as Plaintiff Ceriani may receive BRAC*Analysis*® testing at no charge.

34. Plaintiffs also alleged that the cost of the BRAC*Analysis*® test is too high because of patent exclusivity. However, the HHS Secretary's Advisory Committee on Genetics, Health, and Society ("SACGHS") in March 2009 released a Public Consultation Draft Report on Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests. This Draft Report clearly stated: "One surprising finding from the case studies was that the per-unit price of the full-sequence *BRCA* test, which often is cited as being priced very high, was actually quite comparable to the price of other full-sequence tests done by polymerase chain reaction (PCR), at both nonprofit and for-profit testing laboratories."[22]

35. In fact, the relative price of BRAC*Analysis*® is actually lower than the gene sequencing-based genetic tests offered by those diagnostic labs run by the geneticist plaintiffs Kazazian and Ganguly (the Genetic Diagnostic Laboratory at the University of Pennsylvania), and Ledbetter and Warren (Emory Genetics Laboratory). For example, for full sequencing of the *APC* gene to detect mutations predictive of familial adenomatous polyposis (FAP), a type of hereditary colon cancer, Drs. Kazazian and

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[22] Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS), Public Consultation Draft Report on Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests (2009), http://oba.od.nih.gov/oba/SACGHS/SACGHS%20Patents%20Consultation%20Draft%203%209%202009.pdf.

Ganguly charge $1,360 per test, while Drs. Ledbetter and Warren charge $1,675. Full sequencing genetic tests typically are done exon by exon.[23] The *APC* gene has 15 coding exons, and their prices on a per exon basis are $90.6/exon and $111.7/exon, respectively. In contrast, the *BRCA1* and *BRCA2* genes have 48 total coding exons. The price of Myriad's comprehensive BRAC*Analysis*® test on a per exon basis is less than $70/exon, and this price also includes additional testing for common large genomic rearrangements, which Plaintiffs' tests do not include. *See* Exhibits 5 & 6.

36. Protected by patent exclusivity, Myriad has also made tremendous investment in its clinical laboratory facilities and processes, resulting in great efficiency which is translated into extremely sensitive and accurate tests results which are rendered in a prompt timely fashion to allow health care practitioners to make immediate medical management decisions. Plaintiffs' allegation that patents increase genetic testing cost is simply baseless.

III. PATENTS HAVE PROVIDED INCENTIVE TO IMPROVE TEST QUALITY

37. Myriad is the pioneer and leader in genetic testing. At Myriad, we understand the importance of the quality of our tests better than anyone in the field. That is why from the very beginning Myriad

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[23] An exon is a segment of a gene that corresponds to a portion of an mRNA which encodes part of a protein. In contrast, an intron is the "junk" DNA between two exons. Intron sequences are not in an mRNA and thus do not encode protein sequence.

adopted the full sequencing method in our BRAC*Analysis*® test, the most reliable and sensitive approach, even though it was more expensive. Our method has been independently validated and is recognized throughout the field as the "gold standard."[24] Even so, we have continuously invested in improving the BRAC*Analysis*® test.

Myriad's Full Sequencing Approach in BRAC*Analysis*® Has Been Recognized as the Gold Standard

38. In mid-1990s, Myriad and its collaborators identified the *BRCA1* and *BRCA2* genes, isolated them, and discovered that mutations in the genes are predictive of a predisposition to breast and ovarian cancers. A mutation is an alteration at a chemical unit or units (nucleosides) of a DNA molecule representing a gene.[25]

39. Each of the *BRCA1* and *BRCA2* genes includes segments of DNA called exons and introns. An intron is an intervening segment between two adjacent exons. When a gene is expressed inside cells, the gene is transcribed into a RNA molecule based on the nucleotide structure of one strand of the genomic DNA of the gene. The transcribed RNA molecule is then "spliced" by cutting out the introns

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[24] *See* Eng *et al.* on behalf of the Steering Committee of the Breast Cancer Information Core (BIC) Consortium, *Interpreting Epidemiological Research: Blinded Comparison of Methods Used to Estimate the Prevalence of Inherited Mutations in* BRCA1, J. MED. GENET., 38:824–833 (2001).

[25] There are four different chemical units in DNA molecules: deoxyadenosine ("A"), deoxythymine ("T"), deoxycytosine ("C") and deoxyguanine ("G").

and connecting the adjacent exons together producing a messenger molecule called "mRNA." Thus an mRNA only contains exons but not introns. A protein is encoded by an mRNA. Therefore, a mutation in the genomic DNA of a gene can cause a corresponding change in the mRNA, which may lead to an alteration in the structure of the encoded protein. Some mutations are "insertion or deletion" of a small number of nucleotide units in an exon. Other mutations are "substitutions" of one type of nucleotide unit to a different type of nucleotide unit (e.g., deoxyadenosine to deoxythymidine). Still other mutations are a deletion or duplication of one or more exons, also known as "large genomic rearrangements" or "large rearrangements." Large rearrangements in the *BRCA1* or *BRCA2* gene almost invariably cause major structural alterations in the encoded protein and a loss of function of the protein. They are usually associated with a predisposition to breast and ovarian cancer, i.e., they are "deleterious." Many insertions, deletions, and substitutions result in a frameshift or stop codon causing a truncation of the encoded protein. These kinds of insertions, deletions or substitutions are also deleterious.

40. To detect a mutation in the *BRCA1* and *BRCA2* genes, a tissue sample (e.g., blood) is obtained from a patient. The genomic DNA-containing cells in the sample are broken up, and a sufficient amount of the genomic DNA corresponding to the *BRCA1* and *BRCA2* genes is obtained from the sample. This step typically involves enzymatic synthesis to connect different nucleotide molecules into a DNA chain using a genomic DNA molecule from the patient sample as a template. To obtain a

sufficient quantity of the genomic DNA, the enzymatic synthesis is performed by PCR (polymerase chain reaction) to duplicate the DNA molecule exponentially. However, there is a limit in the size of the genomic DNA fragment that can be made by PCR (about several hundred base pairs). The *BRCA1* and *BRCA2* genes are large in size each being over 70,000 base pairs long, and can not be amplified or duplicated into a single DNA fragment. Under the current state of the art, the only practical way to obtain a sufficient amount of *BRCA1* or *BRCA2* genomic DNA for mutation detection purpose is to PCR amplify the genomic DNA in segments. Typically, each coding exon (an exon that codes for part of the protein sequence) of the *BRCA1* and *BRCA2* genes, including a small adjacent portion of the flanking introns, is separately amplified by PCR into one or more amplified DNA fragments, also called "amplicons." The *BRCA1* and *BRCA2* genes have a total of 48 coding exons containing over 15,700 nucleotide base pairs. More than 50 amplicons are typically produced, and each is subsequently interrogated for the presence or absence of mutations.

41. A mutation can occur in virtually every one of the more than 15,700 nucleotides in the amplicons. Thus, a mutation detection method must be able to identify tens of thousands of mutations distributed along the lengths of the amplicons. There are a number of different methods in the art for mutation detection in the amplicons. At Myriad, we have been using direct nucleotide sequence analysis or "full sequencing." That is, the identity of every single nucleotide unit in the amplicons is determined by sequencing all of the more than 50 amplicons.

Moreover, each amplicon is a double-stranded DNA molecule, and the sequence of one strand can be used to deduce the sequence of the other strand. We determine the sequences of both strands for each amplicon. Additionally, each person has two copies of the *BRCA* genes, and our tests can determine the sequences of both copies. Thus, we have built-in quality control and confirmatory components for every amplicon. Moreover, once a mutation is detected in an amplicon, the entire amplification and sequencing process is repeated for that amplicon to further confirm the mutation. Understandably, the cost associated with this method is high because of the large amount of reagents for sequencing all amplicons as well as the labor required to analyze the more than 30,000 (>15,700 x 2) sequencing data points generated. However, Myriad believes and researchers concur that this method is required to produce a "gold standard" test.

42. In contrast, many other laboratories use shortcut methods. Many of these shortcut methods cost less than the full sequencing approach by Myriad, but have been shown to be inferior in test quality.[26] In many of these methods, all the nucleotide identities in the amplicons are not determined. That is, the methods do not closely examine each nucleotide in the amplicons. Instead, they take a quick and cursory review of each amplicon by an indirect approach. Specifically, they

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[26] Eng *et al.* on behalf of the Steering Committee of the Breast Cancer Information Core (BIC) Consortium, *Interpreting Epidemiological Research: Blinded Comparison of Methods Used to Estimate the Prevalence of Inherited Mutations in* BRCA1, J. MED. GENET., 38:824–833 (2001).

try to predict the presence or absence of mutations in each amplicon based on whether there are any specific physical property changes in the amplicon as a whole. For example, in the CSGE (Conformation-Sensitive Gel Electrophoresis) approach used by Plaintiffs Kazazian and Ganguly in the late 1990s for mutation detection in *BRCA1* and *BRCA2*, the amplicons are run through gel electrophoresis to identify amplicons exhibiting an abnormal migration pattern compared to a normal amplicon. Only those particular amplicons are then sequenced to specifically identify the mutations in the amplicons if any. If no amplicon is detected with an abnormal migration pattern in a patient's sample, no sequencing is performed at all.

43. Because few, if any, of more than 50 amplicons are sequenced, the CSGE method is less expensive. However, the method is significantly less sensitive. In fact, in one comparative study by the Breast Cancer Information Core (BIC) Consortium, the CSGE laboratory participating in the study missed as many as 40% of mutations in *BRCA1* and *BRCA2*.[27] In that study, four different less expensive methods were compared to Myriad's method. Myriad's full sequencing approach was recognized as the "gold standard" for mutation detection for *BRCA1* and *BRCA2*.[28]

Myriad Has Been Continuously Improving Its Testing Process

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[27] *Id.*

[28] *Id.*

44. Relying on strong patent protection, Myriad invested significantly in its testing facilities and testing process from the very beginning. All our tests are done in a highly automated and CLIA-compliant laboratory with utmost quality. Indeed, quality control is one of the most important functions in our testing labs, and we have a large team of quality specialists vigilantly scrutinizing the quality of all our tests. Myriad participates in the College of American Pathologist (CAP) Proficiency Test every year, and has consistently excelled in theses tests.

45. In our process, all tests must be ordered through healthcare providers, and genetic counseling and patient informed consent are prerequisites of all of our *BRCA* mutation testing. These measures have ensured that patients receive the best services from Myriad and develop the best understanding about their test results.

46. The high quality of Myriad's BRAC*Analysis*® test is even more remarkable in view of the very rapid turn-around time required for clinical decision-making. Test results are typically available for patients and healthcare providers within about 2 weeks after the samples are released to Myriad's laboratories. This is in stark contrast to the poor turn-around in *BRCA* testing in Europe. For example, in the UK, it has been reported that some women have to wait up to 2 years for their *BRCA* testing results.[29] Another problem in European

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[29] *See* Laura Barton, *Genetic Testing for Breast Cancer Varies across UK*, LANCET ONCOL., 7:113 (2006); *see also*, BBC News: Health, *Long Wait for Cancer Test Results*, BBC NEWS, Dec. 14, 2005, http://news.bbc.co.uk/2/hi/health/4525260.stm.

BRCA testing is that the test criteria for selecting candidates for *BRCA* testing are much more restrictive than those in the US.[30] As a result, it is estimated that more than 50% of individuals carrying harmful *BRCA* mutations can be missed.[31]

47. Relying on strong patent protection, Myriad has also continuously invested in its testing laboratory to improve the testing process. For example, Myriad has a large in-house team of software programmers and bioinformaticists continuously optimizing our automation process and software.

Large Rearrangement Mutations

48. As explained above in Paragraphs 40 and 41 above, full sequencing analysis requires separate PCR amplification and DNA sequence analysis of each exon and the flanking intronic sequences. The *BRCA1* and *BRCA2* genes have 48 coding exons. In some patients, one or more full exons are deleted or duplicated in one copy of the gene, while the other copy is normal. Because of the normal copy, the deletion or duplication of exons ("large rearrangement") is undetectable by full sequencing.

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[30] *See* Balmaña *et al.*, *BRCA in Breast Cancer: ESMO Clinical Recommendations*, ANN. ONCOL., 20(4):iv19-iv20 (2009); *see also* Wylie Burke, *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care*, N. ENG. J. MED. 358:318 (2008) (book review).

[31] *See* Moller *et al.*, *Genetic Epidemiology of* BRCA *Mutations – Family History Detects Less Than 50% of the Mutation Carriers*, EUR. J. CANCER, 43:1713-1717 (2007).

49. In the late 1990s, Myriad and the research community recognized the need for testing "large rearrangements" in the *BRCA1* and *BRCA2* genes. Large genomic rearrangements occur in a small percentage of all patients tested for hereditary breast and ovarian cancer. Nevertheless, Myriad immediately began researching and developing a commercially viable high quality process for detecting large rearrangements in the genes. As a result, in 2002 Myriad supplemented its full sequencing analysis with a large rearrangement panel (LRP) for detecting five common large rearrangement mutations. Since then, Myriad has included the LRP panel in every comprehensive BRAC*Analysis*® test it performs.

50. In the meantime, Myriad continued its research and development work with a goal to provide a test that could detect all large rearrangement mutations, even those extremely rare ones. The commercially available MLPA (Multiplex Ligation-dependent Probe Amplification) kit often used by academic researchers is for research use only and not approved for clinical testing by the FDA. Moreover, it is incapable of detecting certain rearrangements with smaller sizes, and may yield false positive results for apparent deletions due to nucleotide changes at probe binding sites.

51. After much research and development, Myriad launched in 2006 the BART™ (BRAC*Analysis*® Rearrangement Test) assay which can detect virtually all large rearrangement mutations in the *BRCA1* and *BRCA2* genes. BART™ is a complex quantitative multiplex PCR assay examining every single coding exon and promoter of the *BRCA1* and

BRCA2 genes for large rearrangements. It incorporates an automated and computerized analysis, includes quality control processes to confirm positive results, and has been fully validated and is performed in our CLIA certified, CAP accredited laboratory. In studies by outside researchers, BART™ has exhibited superior performance over other methods including MLPA.[32] Since 2004, Myriad has been sharing information on BART™ with researchers and clinicians in numerous scientific meetings of the Association for Molecular Pathology, the American Society of Human Genetics, and the American Society of Clinical Oncology, among others.

52. BART™ is a complex test with a high cost, and large genomic rearrangements occur in a small percentage of all patients tested for hereditary breast and ovarian cancer. Nevertheless, Myriad has made BART™ available to all patients who want to be tested. At the present time, for high risk patients, BART™ is performed together with our full sequencing analysis and LRP (for common large rearrangements) at no additional charge. For low risk patients who do not meet certain clinical criteria developed based on published literature, BART™ is still available at a reasonable cost.

53. Today, Myriad is still investing heavily to develop a new version of BART™ with a significantly lowered cost and increased efficiency. In these

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[32] *See* Palma *et al.*, *The Relative Contribution of Point Mutations and Genomic Rearrangements in* BRCA1 *and* BRCA2 *in High-Risk Breast Cancer Families*, CANCER RES., 68: 7006-7014 (2008).

efforts. Myriad is working to provide an improved BART™ that is commercially viable to all patients at little cost. Without patent protection, Myriad would not have made such investments.

Variants of Uncertain Clinical Significance

54. Genetic variants of uncertain clinical significance, also known as "VUS", are mostly missense changes and variants that occur in intronic regions whose clinical significance has not yet been determined. Many nucleotide substitutions in the coding exons of the *BRCA* genes result in a change from one amino acid residue to another in the encoded protein. Given the current state of scientific knowledge, it may not yet be possible to determine whether such an amino acid substitution will result in enough changes in protein function to confer an increased risk of breast and ovarian cancer, requiring further scientific research and analysis. There are also other nucleotide substitutions or small insertions or deletions in the *BRCA* genes that occur in an intron. Again, given the current state of science, it can be difficult to determine whether they result in sufficient changes in the protein so as to confer an increased risk of breast and ovarian cancer. All of these mutations are called "variant of uncertain significance" or "VUS."

55. When Myriad detects a VUS, it reports the variant to the patient as a "genetic variant of uncertain significance." The uncertainty about the cancer risk of such variants at the time of their detection arises not because of any limitation in the test, but because of the limits of current scientific knowledge. This is independent of the testing method. Any lab uncovering the same variant, such

as those of Plaintiffs Ledbetter or Ganguly, would need to report the exact same result because of limited scientific knowledge.

56. In fact, there is widespread consensus among cancer geneticists that the VUS problem is challenging. It has been estimated that about one-third of the genetic variants in *BRCA1* and 50% of those found in *BRCA2* reported by the Breast Cancer Information Core (BIC) Consortium are or have been considered genetic variants of unknown clinical significance.[33] Also, the VUS problem is not unique to *BRCA* testing. It is also common in many other genetic tests such as sequencing analysis of the *CFTR* gene (for cystic fibrosis),[34] the *MLH1* and *MSH2* genes (for hereditary nonpolyposis colorectal cancer),[35] the *CDKN2A* gene (for hereditary

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[33] Gómez-García *et al., A Method to Assess the Clinical Significance of Unclassified Variants in the* BRCA1 *and* BRCA2 *Genes Based on Cancer Family History*, BREAST CANCER RES., 11:R8 (2009), http://breast-cancer-research.com/content/11/1/R8; *see also*,

[34] Oca *et al., Amniotic Fluid Digestive Enzyme Analysis Is Useful for Identifying* CFTR *Gene Mutations of Unclear Significance*, CLIN. CHEM., 55:2214-7 (2009).

[35] Arnold *et al., Classifying* MLH1 *and* MSH2 *Variants Using Bioinformatic Prediction, Splicing Assays, Segregation, and Tumor Characteristics*, HUM MUTAT., 30:757-70 (2009); *see also*, Chan *et al., Interpreting Missense Variants: Comparing Computational Methods in Human Disease Genes CDKN2A*, MLH1, MSH2, MECP2, *And Tyrosinase* (TYR), HUM MUTAT. 28:683-93 (2007).

melanoma).[36] and the *APC* gene (for familial adenomatous polyposis or FAP)[37].

57. Over the years, Myriad has continuously invested significant resources in solving the VUS problem. In this regard, Myriad's enormous centralized mutation database based on clinical testing of hundreds of thousands of patients has proven to be critical. Myriad has also made critical data available to noted international researchers and helped them analyze their VUS models in their research.[38] The published research results have the potential of improving the diagnostic testing for the other genes discussed above.

58. Myriad has an in-house review committee for variant classification, and has developed a systematic approach to provide clinical interpretations for detected sequence variants based on generally accepted scientific data and analysis of its own database. We also continuously improve

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[36] Chan *et al.*, *Interpreting Missense Variants: Comparing Computational Methods in Human Disease Genes* CDKN2A, MLH1, MSH2, MECP2, *And Tyrosinase* (TYR), HUM MUTAT. 28:683-93 (2007).

[37] Aretz *et al.*, *Familial Adenomatous Polyposis: Aberrant Splicing Due to Missense or Silent Mutations in the* APC *Gene*, HUM MUTAT. 24:370-80 (2004).

[38] *See e.g.*, Abkevich *et al.*, *Analysis of Missense Variation in Human* BRCA1 *in the Context of Interspecific Sequence Variation*, J. MED. GENET., 40:492-507 (2004); Goldgar *et al.* & Breast Cancer Information Core (BIC) Steering Committee, *Integrated Evaluation of DNA Sequence Variants of Unknown Clinical Significance: Application to* BRCA1 *and* BRCA2, AM. J. MED. GENET., 75:535-544 (2004).

upon this approach based on research advances and accumulated experience. Because of all these efforts, the VUS reporting rate at Myriad has decreased markedly, as we reported recently.[39] In particular, between 2002 and 2006, a decrease of almost 50% was accomplished in major ethnic minority groups.[40] Myriad's extensive *BRCA* testing experience and its centralized clinical data have made large-scale VUS reclassification possible. Today, the overall VUS reporting rate in our *BRCA* testing is below 6.6%, which is significantly lower than that in other tests such as those for the *MLH1* and *MSH2* genes.

59. In addition, Myriad constantly reexamines all remaining VUS previously reported to patients in an attempt to clarify the clinical significance of the variants based on new information gained in research and clinical testing. As soon as a clarification is accomplished for a patient, we generate and send an updated report to the patient's healthcare provider, thus providing the doctor and patient with the most up-to-date scientific information about that patient's particular hereditary cancer risk. In fact, it is estimated that Myriad has in total clarified about 850 VUS for about 21,000 patients, all of whose physicians have been notified with an updated report. Just between the beginning of 2008 and the present, we have thus reclassified 502 VUS for 13,127 patients.

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[39] *See* Hall *et al.*, *BRCA1* and *BRCA2* Mutations in Women of Different Ethnicities Undergoing Testing for Hereditary Breast-Ovarian Cancer, CANCER, 115(10):2222-33 (2009).

[40] *See id.*

60. Clearly, without strong patent protection, Myriad would not have made these enormous investments and would not have been able to make such significant contributions to the progress of science in VUS. Nor would Myriad have been able to accomplish the significant improvement on test quality, particular the reduction of VUS reporting rate and the clarification of test results for tens of thousands of patients.

IV. SECOND OPINION

61. Plaintiffs raised the hypothetical issue of "second opinion." However, in reality, since Myriad launched its BRAC*Analysis*® in 1996, I am not aware of a single request (or even the suggestion) made to Myriad by anyone to seek "second opinion" repeat testing at another lab. In fact, physicians using our test for their patients do not feel the need for a "second opinion" testing. *See* D. Frieder, ¶ 11; D. Bone, ¶ 8. I believe this is largely attributable to the excellent quality of the BRAC*Analysis*® test that patients and their doctors trust. As I discussed in Paragraph 41 above, all BRAC*Analysis*® tests at Myriad already include multiple built-in confirmatory components. Moreover, it simply does not make good economic or medical sense for patients to routinely obtain second opinion testing. Finally, nothing prevents patients from seeking second opinions with genetic counselors and physicians on their test results.

62. In any event, the argument made by the Plaintiffs Girard and Limary, that they cannot get a second test to confirm their *BRCA* mutations, is disingenuous. There are multiple laboratories

available for confirmatory testing under patent licenses from Myriad. Many of these labs have been performing testing for specific *BRCA* mutations for the past ten years. For example, testing for specific *BRCA* mutations is available in both the University of Chicago Genetic Services Laboratories and Yale DNA Diagnostic Laboratories.[41] Information on their testing services for *BRCA* mutations is readily accessible on Internet.[42] Both could provide a confirmatory test for the *BRCA* mutations Plaintiffs Girard and Limary had previously received.

63. If the plaintiffs are still not happy after such second opinion testing, there are also other options for second opinion testing: At any given time, there are a number of research studies going on in the US and abroad by researchers outside Myriad. Plaintiffs can always participate in such research studies for second opinions.

64. Myriad has never prohibited a "second opinion" on *BRCA* mutation testing, which has been available to patients like Plaintiffs Girard and

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[41] Indeed, it is rather disingenuous for plaintiffs to make the allegation of lack of second opinion testing when one of the plaintiffs, Ellen Matloff, the Director of the Cancer Genetic Counseling Program at Yale, works closely with Yale DNA Diagnostic Laboratories from which the hypothetical second opinion testing would be available.

[42] *See* Yale DNA Diagnostic Services: BRCA, http://info.med.yale.edu/genetics/DNA/BRCA-Familial.html (last visited Dec. 17, 2009); *and* Department of Human Genetics, University of Chicago: BRCA Sample Submission Form, http://genes.uchicago.edu/LabPDF/01BRCA.pdf (last visited Dec. 17, 2009).

Limary since late 1990s. In reality, the need for a second opinion is extremely rare and the problem of getting second opinions simply does not exist. It is merely plaintiffs' conjecture for the sole purpose of attacking the US patent system in this suit.

V. CONCLUSION

65. In summary, Myriad's discovery of the *BRCA1* and *BRCA2* genes made clinical testing possible to detect genetic predispositions to breast and ovarian cancers. Early detection of such cancer risks enables patients to utilize various available means to reduce the risks or even possibly prevent cancer. Myriad has consistently encouraged, promoted and subsidized research on the *BRCA* genes, and Myriad's patent rights have not stifled research. As evidence, Myriad has provided *BRCA1* and *BRCA2* cDNA clones free to researchers at over 30 research institutions, and conducted collaborative research with more than 440 scientists all over the world. Overall, more than 18,000 scientists have researched on *BRCA1* and *BRCA2*, and published more than 7,000 papers on the genes since Myriad's publication of the genes. These include 4 plaintiffs in this suit and their supporting declarants publishing a total of 48 papers on *BRCA1* and *BRCA2*.

66. Myriad has performed over 400,000 BRAC*Analysis*® tests for *BRCA* mutations for patients in all 50 states. Over 40,000 healthcare providers have ordered the test. Test results are typically available within two weeks. More than 90% of the BRAC*Analysis*® tests are covered by insurance. There are more than 2,600 insurance payors who reimburse for the BRAC*Analysis*® test. There are

more than 80,000 insurance plans that cover the BRAC*Analysis*® test. The average reimbursement rate is over 90% of the cost of the test. All these accomplishments are directly attributable to Myriad's investment of more than 200 millions of dollars in insurance coverage. and more importantly in raising patient and physician awareness and understanding of the test. Myriad would not have made the investment without the protection by the exact patents plaintiffs are challenging. Myriad's patent rights have clearly promoted patient access to the BRAC*Analysis*® test.

67. Patent rights have also provided incentives for Myriad to continuously invest significantly in its testing facilities and testing process. Testing services are available at Myriad for detecting all mutations in the *BRCA1* and *BRCA2* genes, including rare large rearrangement mutations. Myriad also has the best resources and capability in classifying variants of uncertain clinical significance. Myriad's full sequencing test has been recognized as the "gold standard" for *BRCA* mutation testing. In contrast, the CSGE method used by Plaintiffs Kazazian and Ganguly in the late 1990s has been shown to be unreliable, missing 40% of mutations in *BRCA1* and *BRCA2*.

68. Clearly, Myriad's patent rights have encouraged research on the *BRCA* genes, promoted patient access to *BRCA* testing, and improved the quality of *BRCA* testing at Myriad. For these reasons, Myriad cherishes and respects the US patent system and firmly believes that patent protection for landmark inventions such as the *BRCA1* and *BRCA2* and their use in diagnostic

testing, stimulates innovation and encourages the commercialization and wide dissemination of valuable products and services, and thus provides great benefit to both individuals and society.

Pursuant to 28 USC § 1746, I declare under penalty of perjury that the foregoing is true and correct.

/s/ Gregory C. Critchfield

Gregory C. Critchfield, M.D., M.S.

Executed on December 18, 2009

EXHIBITS 1-6

[EXHIBITS 1-6 OMITTED]

[Declaration of Dr. Mark Kay, filed December 23, 2009] [Caption Omitted In Printing] [Exhibits 1, 2 omitted]

I, Mark Allan Kay, hereby declare that:

I. BACKGROUND AND EXPERIENCE

1. I am currently a tenured professor and Director of the Program in Human Gene Therapy at Stanford University School of Medicine. I am the Dennis Farrey Family Professor in the Departments of Pediatrics and Genetics at Stanford University. I am also the Associate Chair for Basic Research in the Department of Pediatrics at Stanford University School of Medicine. My qualifications, expertise, and list of publications are set forth in my *curriculum vitae* which is attached as Exhibit 1.

2. I received my Ph.D. in Developmental Genetics and my M.D. from Case Western Reserve University in 1986 and 1987, respectively. I completed my internship and residency in the Department of Pediatrics at the Baylor College of Medicine, Houston, Texas in 1990. Between 1990 and 1993, I was a medical genetics fellow at Baylor College of Medicine where I completed clinical training to be Board eligible in both Clinical Medical Genetics and Biochemical Genetics. During those three years, I also completed my post-doctoral research on gene therapy for hepatic deficiencies at Baylor College of Medicine, Houston, Texas.

3. I was triple-boarded: Pediatrics from 1990 until 1997; Clinical Genetics, and Clinical Biochemical Genetics from 1993 until 2003. In my medical practice, I have seen many patients for

diagnosis, recurrence risk, and/or treatment of genetic disorders between 1990 and 1998. Currently, I am involved in Phase I / II clinical trials in gene therapy.

4. My research focuses primarily on developing gene transfer technologies for gene therapy of genetic and acquired diseases of the liver. The second major focus of my research includes the role of small RNAs in mammalian gene regulation.

5. I keep abreast of ongoing research developments in the area of molecular biology and gene therapy by regular perusal of the relevant literature and my service on the editorial boards of several different scientific journals. In particular, I am or have been on the editorial boards of numerous scientific journals, including *Gene Therapy*, *Human Gene Therapy*, and *Molecular Therapy*. I am currently the Associate Editor of *Human Gene Therapy*, *Molecular Therapy*, and *Silence*.

6. In preparing this declaration, I have reviewed the following: (1) Declaration of Sir John E. Sulston, Ph.D. of August 17, 2009 ("Sulston"); (2) Declaration of Christopher E. Mason of August 20, 2009 ("Mason"); (3) Declaration of Wayne W. Grody, M.D., Ph.D. of August 24, 2009 ("Grody"); (4) Declaration of Debra G.B. Leonard, M.D., Ph.D. of August 24, 2009 ("Leonard"); Declaration of Wendy Chung, M.D., Ph.D. of July 30, 2009 ("Chung"); Declaration of Myles W. Jackson of August 18, 2009 ("Jackson"); Declaration of David H. Ledbetter, Ph.D. of August 20, 2009 ("Ledbetter"); and Declaration of Haig H. Kazazian, Jr., M.D. of August 17, 2009 ("Kazazian"). Specifically, I have been asked to comment on the scientific statements contained in these declarations.

7. I have also read the claims, specification, and portions of the prosecution file histories of United States Patent Numbers 5,753,441 (the "'441 patent"); 5,747,282 (the "'282 patent"); 5,710,001 (the "'001 patent"); 5,709,999 (the "'999 patent"); and 5,693,473 (the "'473 patent"), which relate to *BRCA1*, hereinafter referred to as the "*BRCA1* patents," and the claims, specification, and portions of the prosecution file histories of United States Patent Numbers 6,033,857 (the "'857 patent") and 5,837,492 (the "'492 patent"), which relate to the *BRCA2*, hereinafter referred to as the "*BRCA2* patents."

8. I have also reviewed portions of the following textbooks: Bruce Alberts *et al.*, Molecular Biology of the Cell, Third Edition, Garland Publishing, Inc., New York, NY, 1994 ("Alberts") and Lubert Stryer, Biochemistry, Third Edition, W.H. Freeman And Company, New York, NY, 1988 ("Stryer").

9. I have also read the article by Dr. John E. Sulston entitled "Heritage of humanity" published in *Le Monde diplomatique*, English Edition, in 2002 ("Sulston, 2002;" Exhibit 2).

10. I have been asked to provide my opinion from the perspective of one of ordinary skill in the art as of 1994 with respect to the *BRCA1* patents and as of 1995 with respect to the *BRCA2* patents. One of ordinary skill in the art at that time would have been someone with a Ph.D. and several years of postdoctoral experience in the areas of genetics, molecular biology, and/or biochemistry.

II. DEFINITIONS

11. I have been asked to provide my opinion regarding the meaning of certain terms that appear

in the claims of the *BRCA1* and the *BRCA2* patents. Such terms are found in, for example, claims 1, 2, 5, 6, 7, and 20 of the '282 patent; claims 1, 6, and 7 of the '492 patent; claim 1 of the '473 patent; claim 1 of the '999 patent; claim 1 of the '001 patent; claim 1 of the '441 patent; and claims 1 and 2 of the '857 patent. I have been advised and understand that certain claims, known as "dependent" claims, can refer to earlier claims, known as "independent" claims, and that the dependent claims are to be interpreted to incorporate all the limitations of the claim to which it refers.

12. I have been advised and understand that claim terms are generally given their ordinary and customary meaning, *i.e.*, the meaning that the terms would have to a person of ordinary skill in the art at the time of filing of the patent application. I also understand that claim terms must be read in the context of the claims, the specification, and the prosecution history, and, when the specification specifically defines a claim term, that definition controls.

13. I have reviewed the '473 Patent, the '282 Patent, and the '492 Patent, each of which has claims reciting the terms **"DNA"** or **"DNA molecule**." Specifically, these terms are recited in claim 1 of the '473 Patent, claims 1, 2, 5, 6, and 7 of the '282 Patent, and claims 1, 6, and 7 of the '492 Patent.

14. One of skill in the art as of the time of the filing dates of these patents would understand the term "**DNA**," which stands for **d**eoxyribo**n**ucleic **a**cid, to mean a type of chemical compound called a nucleic acid. At its most basic level, a DNA molecule is composed of several chemical elements, namely

Carbon, Hydrogen, Oxygen, Nitrogen, and Phosphorus. These chemical elements make up repeating units that are connected to form a strand or polymer of the DNA molecule. These repeating units of DNA are known as nucleotides. The standard nucleotides in vertebrate DNA contain four different bases: Adenine, Thymine, Cytosine, and Guanine. These bases are linked together by chemical bonds via a sugar-phosphate backbone. As shorthand for convenience, scientists often denote nucleotides by the first letter of the names of their bases: "A" for Adenine; "G" for Guanine; "T" for Thymine; and "C" for Cytosine. DNA can exist as single strand or as double strand molecule. *See, e.g.*, Stryer at pages 71-73.

15. I have found nothing in the specification or prosecution history of the '473 Patent, the '282 Patent, or the '492 Patent that would contradict or alter this definition. The use of "DNA" and "DNA molecule" in the patents is consistent with the ordinary and customary use of the terms in the field of biotechnology.

16. I have reviewed the '473 Patent, the '282 Patent, and the '492 Patent, each of which has claims reciting the term **"isolated DNA."** Specifically, these terms are recited in claim 1 of the '473 Patent; claims 1, 2, 5, 6, and 7 of the '282 Patent; and claims 1, 6, and 7 of the '492 Patent.

17. The term "isolated DNA" is defined in the patents as:

An "isolated" or "substantially pure" nucleic acid (*e.g.*, an RNA, DNA or a mixed polymer) is one which is substantially separated from other cellular components which naturally accompany a native human sequence or protein, *e.g.*, ribosomes, polymerases, many other human genome sequences and proteins. The term embraces a nucleic acid sequence or protein which has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems. '473 Patent, col. 19:6-15; '282 Patent, col. 19:8-18; and '492 Patent, col. 17:62 – col. 18:5.

In other words, someone of ordinary skill in the art would understand that "isolated DNA" has been extracted from the cell and excised from the chromosome, or chemically synthesized. Indeed, an isolated DNA molecule is made by the hand of the scientist, not by nature.

18. I have found nothing in the specification or prosecution history of the '473 Patent, the '282 Patent, or the '492 Patent that would contradict or alter this definition. The term is used according to its specified definition consistently throughout the patents.

19. I have reviewed the '282 Patent and the '492 Patent, each of which has claims reciting the terms **"code for," "coding for," and "encoding."** Specifically, these terms are recited in claim 1 of the '282 Patent and claims 1, 6, and 7 of the '492 Patent.

20. One of skill in the art at the time of the filing dates of these patents would understand that the term "encode" can be used interchangeably with the terms "code for" and "coding for." The term "encode" is defined in the patents as:

A polynucleotide is said to "encode" a polypeptide if, in its native state or when manipulated by methods well known to those skilled in the art, it can be transcribed and/or translated to produce the mRNA for and/or the polypeptide or a fragment thereof. '282 Patent, col. 19:1-5; and '492 Patent, col. 17:55-59.

21. I have found nothing in the specification or prosecution history of the '282 Patent or the '492 Patent that would contradict or alter this definition. The terms are used according to their specified definition consistently throughout the patents.

22. I have reviewed the '473 Patent, the '282 Patent, the '999 Patent, the '001 Patent, and the '441 Patent, each of which has claims reciting one or more of the term "**BRCA1.**" Specifically, this term is recited in claim 1 of the '473 Patent; claims 1 and 20 of the '282 Patent; claim 1 of the '999 Patent; claim 1 of the '001 Patent, and claim 1 of the '441 Patent.

23. The term "**BRCA1**" means a human breast and ovarian cancer predisposing gene, some alleles of which cause susceptibility to cancer, in particular breast and ovarian cancer. (*See, e.g.*, '282 Patent, col. 1: 20-24; 4:32-36).

24. Dr. Grody and Dr. Leonard state that "**BRCA1**" was known to refer to "a particular portion of DNA found on chromosome 17 that relate[s] to a person's predisposition to develop breast and ovarian cancer." Grody ¶19. Leonard ¶39. I would like to clarify, the *BRCA1* gene is an aggregate of several segments of a chromosome. Some segments regulate the activity of the *BRCA1* gene. From other segments, *BRCA1* pre-mRNA and then mRNA is

produced. From the mRNA, BRCA1 protein is typically produced.

25. I have reviewed the '473 Patent, the '282 Patent, the '999 Patent, the '001 Patent, and the '441 Patent, each of which has claims reciting one or more of the terms **"BRCA1 Locus," BRCA1 Gene," "BRCA1 Nucleic Acids,"** and **"BRCA1 Polynucleotide."** Specifically, these terms are recited in claim 1 of the '473 Patent; claim 20 of the '282 Patent; claim 1 of the '999 Patent; claim 1 of the '001 Patent, and claim 1 of the '441 Patent.

26. The meaning of "BRCA1" is further clarified in the Myriad patents:

As used herein, the terms "BRCA1 locus," "BRCA1 allele" and "BRCA1 region" all refer to the double-stranded DNA comprising the locus, allele, or region, as well as either of the single-stranded DNAs comprising the locus, allele or region. '473 Patent, col. 20:53-57; '282 Patent, col. 20:58-62; '999 Patent, col. 20:61-65; '001 Patent, col. 20:61-65; and '441 Patent col. 20:61-65.

"BRCA1 Locus," BRCA1 Gene," "BRCA1 Nucleic Acids," and "BRCA1 Polynucleotide" are defined in these patents as:

> [P]olynucleotides, all of which are in the BRCA1 region, that are likely to be expressed in normal tissue, certain alleles of which predispose an individual to develop breast, ovarian, colorectal and prostate cancers. Mutations at the BRCA1 locus may be involved in the initiation and/or progression of other types of tumors. The locus is indicated

> in part by mutations that predispose individuals to develop cancer. These mutations fall within the BRCA1 region described *infra*. The BRCA1 locus is intended to include coding sequences, intervening sequences and regulatory elements controlling transcription and/or translation. The BRCA1 locus is intended to include all allelic variations of the DNA sequence. These terms, when applied to a nucleic acid, refer to a nucleic acid which encodes a BRCA1 polypeptide, fragment, homolog or variant, including, *e.g.*, protein fusions or deletions. The nucleic acids of the present invention will possess a sequence which is either derived from, or substantially similar to a natural BRCA1-encoding gene or one having substantial homology with a natural BRCA1-encoding gene or a portion thereof. The coding sequence for a BRCA1 polypeptide is shown in SEQ ID NO: 1, with the amino acid sequence shown in SEQ ID NO:2. '473 Patent, col. 19:22-45; '282 Patent, col. 19:25-50; '999 Patent, col. 19:27-52; '001 Patent, col. 19:30-44; and the '441 Patent, col. 19:30-54.

27. One of skill in the art would understand that BRCA1/2 are genes, not fragments of DNA. Genes are integrated into the chromosome and not broken or detached from the chromosome, as denoted by the term "fragment."

28. I have found nothing in the specification or prosecution history of the '473 Patent, the '282 Patent, the '999 Patent, the '001 Patent, or the '441 Patent that would contradict or alter this definition. The terms are used according to their specified definition consistently throughout the patents.

29. I have reviewed the '473 Patent, the '282 Patent, the '999 Patent, the '001 Patent, and the '441 Patent, each of which has claims reciting one or more of the term **"BRCA2."** Specifically, this term is recited in claims 1 and 2 of the '857 Patent; and claims 1 and 6 of the '492 patent.

30. The term **"BRCA2"** means a human breast cancer predisposing gene, some alleles of which cause susceptibility to cancer, in particular breast cancer. (*See*, *e.g.*, '492 patent, col. 4: 26-30).

31. Dr. Grody and Dr. Leonard state that **"BRCA2"** was known to refer to "a particular portion of DNA found on chromosome 13 that relate[s] to a person's predisposition to develop breast cancer." Grody Decl. ¶22. Leonard Decl. ¶42. I would like to clarify, the *BRCA2* gene is an aggregate of several segments of a chromosome. Some segments regulate the activity of the *BRCA2* gene. From other segments, *BRCA2* pre-mRNA and then mRNA is produced. From the mRNA, BRCA2 protein is typically produced.

32. I have reviewed the '492 Patent and the '857 Patent, each of which has claims reciting one or more of the terms **"BRCA2 Locus," BRCA2 Gene," "BRCA2 Nucleic Acids,"** and **"BRCA2 Polynucleotide"** Specifically, these terms are

recited in claims 1, 6, and 7 of the '492 Patent; and claims 1 and 2 of the '857 Patent.

33. The meaning of "BRCA2" is further clarified in the Myriad patents:

As used herein, the terms "BRCA2 locus," "BRCA2 allele," and "BRCA2 region" all refer to the double-stranded DNA comprising the locus, allele, or region, as well as either of the single-stranded DNAs comprising the locus, allele or region. '857 Patent, col. 19:45-49; and '492 Patent, col. 19: 43-47.

The terms "BRCA2 Locus," BRCA2 Gene," "BRCA2 Nucleic Acids," and "BRCA1 Polynucleotide" are defined in the patents as:

> [P]olynucleotides, all of which are in the BRCA2 region, that are likely to be expressed in normal tissue, certain alleles of which predispose an individual to develop breast, ovarian and stomach cancers. Mutations at the BRCA2 locus may be involved in the initiation and/or progression of other types of tumors. The locus is indicated in part by mutations that predispose individuals to develop cancer. These mutations fall within the BRCA2 region described *infra*. The BRCA2 locus is intended to include coding sequences, intervening sequences and regulatory elements controlling transcription and/or translation. The BRCA2 locus is intended to include all allelic variations of the DNA sequence. These terms, when applied to a nucleic acid, refer to a

> nucleic acid which encodes a BRCA2 polypeptide, fragment, homolog or variant, including, *e.g.*, protein fusions or deletions. The nucleic acids of the present invention will possess a sequence which is either derived from, or substantially similar to a natural BRCA2-encoding gene or one having substantial homology with a natural BRCA2-encoding gene or a portion thereof. The coding sequence for a BRCA2 polypeptide is shown in SEQ ID NO:1 and FIG. 3, with the amino acid sequence shown in SEQ ID NO:2. '857 Patent, col. 18:14-37; and '492 Patent, col. 18:12-35.

34. I have found nothing in the specification or prosecution history of the '492 Patent or the '857 Patent that would contradict or alter this definition. The terms are used according to their specified definition consistently throughout the patents.

35. I have reviewed the '282 Patent and the '492 Patent, each of which has one or more claims reciting the "**polypeptide**." Specifically, this term is recited in claims 1, 2, 5, and 6 of the '282 Patent; and claims 1, 6, and 7 of the '492 Patent.

36. The term "polypeptide" is defined in these patents as

> [A] polymer of amino acids and its equivalent and does not refer to a specific length of the product; thus, peptides, oligopeptides and proteins are included within the definition of a

> polypeptide. This term also does not refer to, or exclude modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations, and the like. Included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), polypeptides with substituted linkages as well as other modifications known in the art, both naturally and non-naturally occurring. '282 Patent, col. 21:3-14; and '492 Patent, col. 19:55-66.

37. I have found nothing in the specification or prosecution history of the '282 Patent or the '492 Patent that would contradict or alter this definition. The term is used according to its specified definition consistently throughout the patents.

38. I have reviewed the '282 Patent which has one or more claims reciting the **"BRCA1 polypeptide."** Specifically, this term is recited in claims 1, 2, 5, and 6 of the '282 Patent.

39. The term "BRCA1 polypeptide" is defined in the patents as

> [A] protein or polypeptide encoded by the BRCA1 locus, variants or fragments thereof. ... Ordinarily, such polypeptides will be at least about 50% homologous to the native BRCA1 sequence, preferably in excess of about 90%, and more preferably at least about 95% homologous. Also included are

> proteins encoded by DNA which hybridize under high or low stringency conditions, to BRCAl-encoding nucleic acids and closely related polypeptides or proteins retrieved by antisera to the BRCAI protein(s). The length of polypeptide sequences compared for homology will generally be at least about 16 amino acids, usually at least about 20 residues, more usually at least about 24 residues, typically at least about 28 residues, and preferably more than about 35 residues. '282 Patent, col. 21:1-27.

The sequence of the BRCA1 protein is disclosed (SEQ ID NO:2). *Id.* at col. 34: 41-43.

40. I have found nothing in the specification or prosecution history of the '282 Patent that would contradict or alter this definition. The term is used according to its specified definition consistently throughout the patents.

41. I have reviewed the '492 Patent which has one or more claims reciting the **"BRCA2 polypeptide."** Specifically, this term is recited in claims 1, 6, and 7 of the '492 Patent.

42. The term "BRCA2 polypeptide" is defined in the patents as "BRCA2 protein" or "BRCA2 polypeptide" refer to a protein or polypeptide encoded by the BRCA2 locus, variants or fragments thereof. The term "polypeptide" refers to a polymer of amino acids and its equivalent and does not refer to a specific length of the product; thus, peptides, oligopeptides and proteins are included within the

definition of a polypeptide. This term also does not refer to, or exclude modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations, and the like. Included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), polypeptides with substituted linkages as well as other modifications known in the art, both naturally and non-naturally occurring. Ordinarily, such polypeptides will be at least about 50% homologous to the native BRCA2sequence, preferably in excess of about 90%, and more preferably at least about 95% homologous. Also included are proteins encoded by DNA which hybridize under high or low stringency conditions, to BRCA2-encoding nucleic acids and closely related polypeptides or proteins retrieved by antisera to the BRCA2 protein(s). '492 col. 19:53-20:7.

The sequence of the BRCA2 protein is disclosed (SEQ ID NO:2). *See id.* at col. 18:33-35.

43. I have found nothing in the specification or prosecution history of the '492 Patent that would contradict or alter this definition. The term is used according to its specified definition consistently throughout the patents.

44. I have reviewed the '282 Patent and the '492 Patent, each of which has claims reciting the term **"amino acid sequence."** Specifically, this term is recited in claims 1, 2, 5, and 6 of the '282 Patent, and claim 1 of the '492 Patent.

45. One of skill in the art as of the time of the filing dates of these patents would understand the

term "amino acid sequence" as a description of the linear order of the amino acid subunits in a polypeptide or protein. *See* Stryer, at 16-17. The amino acid sequence of a protein is also called the primary structure of that protein. *See id.* at 31.

46. In the context of the patents, "amino acid sequence" was used to describe polypeptides or proteins, or their encoding polynucleotides via the arrangement of the amino acids. The specific amino acid sequences for particular polypeptides or proteins are generally identified as "SEQ ID NO:X." For example, as described in the patents:

> The coding sequence for a BRCA[1/2] polypeptide is shown in SEQ ID NO:1. with the amino acid sequence shown in SEQ ID NO:2. '282 Patent, col. 19:48-50; '492 Patent, col. 18:33-35.

47. I have found nothing in the specification or prosecution history of the '282 Patent or the '492 Patent that would contradict or alter this definition. The term is used according to its specified definition consistently throughout the patents.

48. I have reviewed the '473 Patent, '282 Patent, '999 Patent, and the '492 Patent, each of which has claims reciting the term **"SEQ ID NO:1."** Specifically, this is recited in claim 1 of the '473 Patent, claims 2, 6, and 7 of the '282 Patent, claim 1 of the '999 Patent, and claim 7 of the '492 Patent.

49. In the context of the BRCA1 patents, the term "SEQ ID NO:1" refers to the nucleotide sequence of the BRCA1 cDNA as depicted in the Sequence Listing of the '473 Patent, the '282 Patent, and the

'999 Patent. As described in Example 8 of the '473 Patent, the '282 Patent, and the '999 Patent:

> Combination of sequences obtained from cDNA clones, hybrid selection sequences, and amplified PCR products allowed construction of a composite full length BRCA1 cDNA (SEQ ID NO: 1). The sequence of the BRCA1 cDNA (up through the stop codon) has also been deposited with GenBank and assigned accession number U-14680. This deposited sequence is incorporated herein by reference. '473 Patent, col. 52:50-56; '282 Patent, col. 53:4-9; and '999 Patent, col. 53:16-22.

50. In the context of the BRCA2 patents, the term "SEQ ID NO:1" refers to the nucleotide sequence of the BRCA1 cDNA as depicted in the Sequence Listing of the '492 Patent. As described in Example 4 of the '492 Patent:

> The full-length sequence of the BRCA2 was assembled by combination of several smaller sequences obtained from hybrid selection, exon trapping, cDNA library screening, genomic sequencing, and PCR experiments using cDNA as template for amplification (*i.e.*, island hopping"). ... This cDNA sequence is set forth in SEQ ID NO:1 and FIG.3. '492 Patent, col. 44:53-col. 45:10.

51. I have found nothing in the specification or prosecution history of the '473 Patent, the '282 Patent, the '999 Patent, and the '492 Patent that

would contradict or alter this definition. The term is used according to their specified definition consistently throughout the patents.

52. I have reviewed the '282 Patent and the '492 Patent, each of which has claims reciting the term **"SEQ ID NO:2."** Specifically, this is recited in claims 1, 2, 5, 6 of the '282 Patent and claims 1, 6, and 7 of the '492 Patent.

53. In the context of the BRCA1 patents, "SEQ ID NO:2" refers to the amino acid sequence of the BRCA1 polypeptide as depicted in the Sequence Listing of the '282 Patent. In the '282 Patent, the BRCA1 polypeptide is defined as having "[t]he coding sequence ... shown in SEQ ID NO:1 with the amino acid sequence shown in SEQ ID NO:2." '282 patent, col. 19:48-50.

54. In the context of the BRCA2 patents, "SEQ ID NO:2" refers to the amino acid sequence of the BRCA2 polypeptide as depicted in the Sequence Listing of the '492 Patent. In the '492 patent, the BRCA2 polypeptide is defined as having "[t]he coding sequence ... shown in SEQ ID NO:1 and FIG. 3, with the amino acid sequence shown in SEQ ID NO:2." '492 patent, col. 18:33-35.

55. I have found nothing in the specification or prosecution history of the '282 Patent and the '492 Patent that would contradict or alter this definition. The term is used according to its specified definition consistently throughout the patents.

56. I have reviewed the '282 Patent which has a claim reciting the term **"transformed eukaryotic host cell."** Specifically, this is recited in claim 20 of the '282 Patent.

57. The '282 patent defines "transformation" as "[t]he introduction of the polynucleotides into the host cell by any method known in the art." '282 Patent, col. 27:28-30. In addition, the '282 patent refers to "host cells which are stably transformed with recombinant polynucleotides." '282 patent, col. 30:67 to col. 31:1. Thus, in the context of claim 20 of the '282 Patent, the term "transformed eukaryotic host cell" refers to a eukaryotic cell where polynucleotides have been introduced into the host cell by any method known in the art.

58. I have found nothing in the specification or prosecution history of the '282 Patent that would contradict or alter this definition. The term is used according to its specified definition consistently throughout the patents.

59. I have reviewed the '473 Patent, the '282 Patent, the '999 Patent, the '001 Patent, and the '441 Patent each of which has a claim reciting the term **"altered"** and **"alteration."** Specifically, this is recited in claim 1 of the '473 Patent, claim 20 of the '282 Patent, claim 1 of the '999 Patent, claim 1 of the '001 Patent, claim 1 of the '441 Patent, and claim 2 of the '857 Patent.

60. The terms "altered" and "alterations" are defined in these patents as

> [A]ll forms of mutations including deletions, insertions and point mutations in the coding and noncoding regions. Deletions may be of the entire gene or of only a portion of the gene. Point mutations may result in stop codons, frameshift mutations or amino

acid substitutions. Somatic mutations are those which occur only in certain tissues, *e.g.*, in the tumor tissue, and are not inherited in the germline. Germline mutations can be found in any of a body's tissues and are inherited. If only a single allele is somatically mutated, an early neoplastic state is indicated. However, if both alleles are somatically mutated, then a late neoplastic state is indicated. The finding of BRCA1 mutations thus provides both diagnostic and prognostic information. A BRCA1 allele which is not deleted (*e.g.*, found on the sister chromosome to a chromosome carrying a BRCA1 deletion) can be screened for other mutations, such as insertions, small deletions, and point mutations. It is believed that many mutations found in tumor tissues will be those leading to decreased expression of the BRCA1 gene product. However, mutations leading to non-functional gene products would also lead to a cancerous state. Point mutational events may occur in regulatory regions, such as in the promoter of the gene, leading to loss or diminution of expression of the mRNA. Point mutations may also abolish proper RNA processing, leading to loss of expression of the BRCA1 gene product, or to a decrease in mRNA stability or translation efficiency. '473 Patent, col. 12:32-58; '282 Patent, col.

12:31-57; '999 Patent, col. 12:33-59; '001 Patent, col. 12:35-61; and '441 Patent, col. 12:39-65.

61. I have found nothing in the specification or prosecution history of the '473 Patent, the '282 Patent, the '999 Patent, the '001 Patent, and the '441 Patent that would contradict or alter this definition. These terms are used according to their specified definition consistently throughout the patents.

62. I have reviewed the '282 Patent, the '001 Patent, the '441 Patent, and the '857 Patent each of which has a claim reciting the term **"comparing."** Specifically, this is recited in claim 20 of the '282 Patent, claim 1 of the '001 Patent, claim 1 of the '441 Patent and claims 1 and 2 of the '857 Patent.

63. In the context of the method of claim 20 of the '282 Patent, the term "comparing the growth rate of said host cells" and wherein one host cell is a "transformed eukaryotic host cell" necessarily involves first transforming the cells, *i.e.*, introducing a polynucleotide into the cell.

64. In the context of the method of claim 1 of the '001 Patent, the term "comparing a first sequence selected form the group consisting of a BRCA1 gene from said tumor sample, BRCA1 RNA from said tumor sample and BRCA1 cDNA made from mRNA from said tumor sample with a second sequence selected from the group consisting of BRCA1 gene from a nontumor sample of said subject, BRCA1 RNA from said nontumor sample and BRCA1 cDNA made from mRNA from said nontumor sample" necessarily involves first isolating nucleic acids from the tumor sample and nontumor sample from the same human

subject and determining the sequence of the BRCA1 gene or portions thereof from both samples. *See* '001 Patent, col. 13:49-59. Once the sequences have been determined, they are examined to identify any somatic changes in the gene.

65. In the context of the method of claim 1 of the '441 Patent, the term "comparing germline sequence of a BRCA1 gene or BRCA1 RNA from a tissue sample from said subject or a sequence of BRCA1 cDNA made from mRNA from said sample with germline sequences of wild-type BRCA1 gene, wild-type BRCA1 RNA or wild-type BRCA1 cDNA" necessarily involves first isolating nucleic acids from the tissue sample of said subject and from a wild-type sample from a different human subject and determining the sequence of the BRCA1 gene or portions thereof from both samples. *See* '441 Patent, col. 13:53-63. Once the sequences have been determined, they are examined to identify any germline alterations in the gene of said subject.

66. In the context of the method of claim 1 of the '857 Patent, the term "comparing the nucleotide sequence of the suspected mutant BRCA2 allele with the wild-type BRCA2 nucleotide sequence" necessarily involves first isolating the suspected BRCA2 allele from the chromosome and a wild-type allele sample, then determining the sequence of the BRCA2 gene or portions thereof from both samples. *See* '857 Patent, col. 26:66 – col. 27:20. Once the sequences have been determined, they are examined to identify any alterations in the suspected BRCA2 allele.

67. In the context of the method of claim 2 of the '857 Patent, the term "comparing the germline

sequence of the BRCA2 gene or the sequence of its mRNA in a tissue sample from said subject with the germline sequence of the wild-type BRCA2 gene or the sequence of its mRNA" necessarily involves first isolating nucleic acids from the tissue sample of said subject and from a wild-type sample from a different human subject and determining the sequence of the BRCA2 gene or portions thereof from both samples. *See* '857 Patent, col. 12:34-44. Once the sequences have been determined, they are examined to identify any germline alterations in the gene of said subject.

68. I have found nothing in the specification or prosecution history of the '001 Patent, the '441 Patent, and the '857 Patent that would contradict or alter this definition. This term is used according to their specified definition consistently throughout the patents.

69. I have reviewed the '999 Patent which has a claim reciting the term **"analyzing."** Specifically, this is recited in claim 1 of the '999 Patent.

70. In the context of the method of claim 1 of the '999 Patent, the term "analyzing a sequence of a BRCA1 gene or BRCA1 RNA from a human sample or analyzing a sequence of BRCA1 cDNA made from mRNA from said human sample with the proviso that said germline alteration is not a deletion of 4 nucleotides corresponding to base numbers 4184-4187 of SEQ ID NO:1" necessarily involves first isolating nucleic acids from a human and determining the sequence of the BRCA1 gene or portions thereof. *See* '999 Patent, col. 64:35-46. Once the sequence has been determined, it is examined to identify where any one of the alterations set forth in Tables 12A, 14, 18 or 19 is present. Accordingly,

analyzing *BRCA1* requires a probe or primer specific to the *BRCA1* gene, RNA, or cDNA to obtain the sequence from the human tissue sample. One of skill in the art would further understand that the step requires using an isolated DNA molecule specific to *BRCA1*, such as a sequencing probe or primer specific to the *BRCA1* gene, *BRCA1* mRNA or *BRCA1* cDNA, to analyze the sequence from the human sample. Without this isolated DNA molecule, the sequence cannot be analyzed. The DNA or RNA of the tissue sample is changed when the isolated *BRCA1* DNA molecule is used to bind to and "hybridize" the DNA or RNA in the human sample. A new "hybrid" DNA/DNA or DNA/RNA compound is formed, allowing its sequence to be analyzed. As a result, the original human sample is no longer the same human sample, and the DNA and mRNA obtained from the human sample are no longer the same DNA and mRNA molecules that were present in the original human sample.

71. I have found nothing in the specification or prosecution history of the '999 Patent that would contradict or alter this definition. This term is used according to their specified definition consistently throughout the patents.

72. I have reviewed '441 Patent and the '857 Patent which has a claim reciting the term **"wild type."** Specifically, this term is recited in claim 1 of the '441 Patent and claims 1 and 2 of the '857 Patent.

73. The terms "wild type" in the context of a *BRCA1* or *BRCA2* sequence refers to the *BRCA1* or *BRCA2* of the non-mutant *BRCA1*- or *BRCA2*-encoding gene. The coding sequence for a *BRCA1* polypeptide is shown in SEQ ID NO:1 with the amino

acid sequence shown in SEQ ID NO:2. *See* '441 Patent, col. 19:48-54; and '857 Patent, col. 18:31-37.

74. I have found nothing in the specification or prosecution history of the '441 Patent and the '857 Patent that would contradict or alter this definition. This term is used according to its specified definition consistently throughout the patents.

75. I have reviewed the '492 Patent and the '857 Patent each of which has a claim reciting the terms **"mutated," "mutant,"** and **"mutation."** Specifically, this is recited in claims 6 and 7 of the '492 Patent and claim 1 of the '857 Patent.

76. The terms "mutated," "mutant," and "mutation" in the context of these patents refer to a change in the sequence of nucleotides found in the DNA molecule relative to the "wild type" sequence. Contrary to Dr. Leonard's statement (Leonard, ¶66), not all mutations result in disease as the term is used in the '492 patent:

> Silent mutations or those resulting in conservative amino acid substitutions would not generally be expected to disrupt protein function. '492 Patent, col. 11:8-10; and '857 Patent, col. 11:11-14.

"Alteration of wild type gene" encompasses all forms of mutations including deletions, insertions and point mutations in the coding and noncoding regions. Deletions may be of the entire gene or of only a portion of the gene. Point mutations may result in stop codons, frameshift mutations or amino acid substitutions. Somatic mutations are those which occur only in certain tissues, *e.g.*, in the tumor tissue, and are not inherited in the germline. Germline mutations can be found in any of a body's tissues and are inherited. If only a single allele is somatically mutated, an early neoplastic state is indicated. However, if both alleles are somatically mutated, then a late neoplastic state is indicated. The finding of BRCA2 mutations thus provides both diagnostic and prognostic information. A BRCA2 allele which is not deleted (*e.g.*, found on the sister chromosome to a chromosome carrying a BRCA2 deletion) can be screened for other mutations, such as insertions, small deletions, and point mutations. It is believed that many mutations found in tumor tissues will be those leading to decreased expression of the BRCA2 gene product. However, mutations leading to non-functional gene products would also lead to a cancerous state. Point mutational events may occur in regulatory regions, such as in the promoter of the gene, leading to loss or diminution of expression of the mRNA. Point mutations may also abolish proper RNA processing, leading to loss of expression of the BRCA2 gene product, or to a decrease in mRNA stability or translation efficiency. '492 Patent, col. 11:16-42; and '857 Patent, col. 11:20-46.

77. I have found nothing in the specification or prosecution history of the '492 Patent and the '857 Patent that would contradict or alter this definition. These terms are used according to their specified definition consistently throughout the patents.

78. I have reviewed the '441 Patent, the '999 Patent, and the '857 Patent each of which has a claim reciting the term **"germline."** Specifically, this is recited in claim 1 of the '441 Patent, claim 1 of the '999 Patent, and claim 2 of the '857 Patent.

79. One of skill in the art as of the time of the filing dates of these patents would understand the term "germline" refers to the lineages of cells that give rise to germ cells, *i.e.*, eggs and sperm cells. *See* Alberts, at G-10. Thus, a mutation in the DNA of a germline cell may be transmitted in the next generation.

80. In the context of the patents, "germline" is used to describe mutations that can be found in any of the body's tissues, *i.e.*, not just the tissue from the tumor, and are inherited. *See* '441 Patent, col. 12:46-47; '999 Patent, col. 12:40-41; and '857 Patent, col. 11:27-28.

81. I have found nothing in the specification or prosecution history of the '441 Patent, the '999 Patent, and the '857 Patent that would contradict or alter this definition. This term is used according to their specified definition consistently throughout the patents.

82. I have reviewed the '441 Patent and the '857 Patent each of which has a claim reciting the term **"germline sequence."** Specifically, this is recited in claim 1 of the '441 Patent and claim 2 of the '857 Patent.

83. One of skill in the art as of the time of the filing dates of these patents would understand the term "germline sequence" refers to a sequence that is inherited. An alteration in a germline sequence can occur in the germ cells anytime in life.

84. According to the '441 patent:

> Germline mutations can be found in any of a body's tissues and are inherited.

See '441 Patent, col. 12:46-47; and '857 Patent, col. 11:27-28.

85. I have found nothing in the specification or prosecution history of the '441 Patent and the '857 that would contradict or alter this definition. This term is used according to their specified definition consistently throughout the patents.

86. I have reviewed the '001 Patent which has a claim reciting the term **"somatic."** Specifically, this is recited in claim 1 of the '001 Patent.

87. One of skill in the art as of the time of the filing dates of these patents would understand the term "somatic" refers to non-germline cells of the body. *See* Alberts, at 1012.

88. In the context of the patents, "somatic" is used to describe mutations that "occur only in certain tissues, *e.g.*, in tumor tissue, and are not inherited in the germline." '001 Patent, col. 12:40-42.

89. I have found nothing in the specification or prosecution history of the '001 Patent that would contradict or alter this definition. This term is used according to their specified definition consistently throughout the patents.

90. I have reviewed the '999 Patent, the '001 Patent, and the '441 Patent each of which have a claim reciting the term **"RNA."** Specifically, this is recited in claim 1 of the '999 Patent, claim 1 of the '001 Patent, and claim 1 of the '441 Patent.

91. One of skill in the art as of the time of the filing dates of these patents would understand the term "RNA" stands for ribonucleic acid. RNA, like DNA, is a chemical compound called a nucleic acid

and is formed by a strand of bases that are linked together via a sugar-phosphate backbone. Unlike DNA, however, the four different bases in RNA uracil, adenine, cytosine, and guanine. Common abbreviations for these chemical compounds are "U" for uracil, "A" for adenine, "C" for cytosine, "G" for guanine. Each base together with one sugar and one phosphate molecule makes up a nucleotide. The structures of the sugar-phosphate backbone of RNA and DNA are also different from each other—while RNA contains a ribose sugar, the sugar component of DNA is a deoxyribose. The different chemical components of RNA and DNA affect their functions and properties. For example, unlike DNA, which forms a double helix, RNA usually exists as a single strand. *See* Alberts, at 4-7, 46-47, 60.

92. In the context of the patents, "RNA" is a subgroup of "the polynucleotide compositions of this invention" (*see* '999 Patent, col. 19:53-54; '001 Patent, col. 19:55-56; and '441 Patent, col. 19:55-56).

93. I have found nothing in the specification or prosecution history of the '999 Patent, the '001 Patent, and the '441 Patent that would contradict or alter this definition. This term is used according to their specified definition consistently throughout the patents.

94. I have reviewed the '999 Patent, the '001 Patent, and the '441 Patent each of which has a claim reciting the term **"cDNA."** Specifically, this is recited in claim 1 of the '999 Patent, claim 1 of the '001 Patent, and claim 1 of the '441 Patent.

95. One of skill in the art as of the time of the filing dates of these patents would understand the

term "cDNA" to mean a DNA molecule that is commonly synthesized from a mature mRNA in a reaction catalyzed by a protein known as reverse transcriptase. cDNA received its name because each base in the cDNA can bind to a base in the mRNA from which the DNA is synthesized. In other words, it is "complementary" to the mRNA from which it is synthesized.

96. I have reviewed the '001 Patent, and the '852 Patent each of which has a claim reciting the term **"mRNA."** Specifically, this is recited in claim 1 of the '001 Patent, in claim 1 of the '999 Patent, in claim 1 of the '441 Patent, and claim 2 of the '857 Patent.

97. One of skill in the art as of the time of the filing dates of these patents would understand the term "mRNA" to mean messenger RNA that functions during the production of protein, *i.e.*, translation, to specify the sequence of amino acids in a polypeptide. In eukaryotes, mRNA is formed in the nucleus from pre-messenger RNA. The pre-messenger RNA molecule is initially transcribed and than processed into mRNA by removing the introns and splicing together some or all of the exons. *See* Alberts at p. 368. Pre-messenger RNA is commonly many times larger than the resulting mRNA. Splicing of a pre-messenger RNA typically occurs concurrently with transcription of the pre-messenger RNA.

98. I have reviewed the '001 Patent which has a claim reciting the term **"cDNA made from mRNA."** Specifically, this is recited in claim 1 of the '001 Patent, in claim 1 of the '999 Patent, and in claim 1 of the '441 Patent.

99. One of skill in the art as of the time of the filing dates of these patents would understand the term "cDNA made from mRNA" to mean a cDNA that is artificially created via the reverse transcription of an mRNA. A cDNA made from an mRNA is structurally and functionally different from the mRNA. While the four bases in cDNA are adenine, cytosine, guanine, and thymine, the four bases in mRNA are uracil, adenine, cytosine, and guanine. Second, the sugar-phosphate backbone in cDNA is chemically different from the sugar-phosphate backbone of mRNA. This difference in structure allows cDNA to form the famous double helix. Around 1994, for genes as large as *BRCA1* or *BRCA2*, the synthesis of cDNA from an mRNA molecule did typically not result in a DNA strand that is as long as the mature RNA chain. Instead, several DNA fragments had to be ligated together to form a full length cDNA. Initially, the cDNA is single stranded but the second strand can be synthesized to form a double stranded cDNA molecule. *See* '999 Patent, col. 52:39-53:19; '001 Patent, col. 52:39-53:19; and '441 Patent, col. 53:1-49.

100. Moreover, cDNA is a much more stable molecule than mRNA. The stable nature of cDNA molecules or fragments of cDNA molecules make them suitable as primers and probes for, *e.g.*, biotechnological and diagnostic applications. Protein can be translated directly from mRNA whereas protein cannot be directly translated from cDNA but requires the additional step of RNA transcription. In the body, tens of thousands different mRNA molecules are present. Synthesized cDNA, on the other hand, is generated in the laboratory commonly as a homogenous population of

molecules of the same kind to study a specific gene of interest.

101. I have found nothing in the specification or prosecution history of the '999 Patent, the '001 Patent, the '441 Patent and the '857 Patent that would contradict or alter this definition. This term is used according to their specified definition consistently throughout the patents.

102. I have reviewed '857 Patent which has a claim reciting the term **"allele."** Specifically, this is recited in claim 1 of the '857 Patent.

103. One of skill in the art as of the time of the filing dates of these patents would understand the term "allele" refers to alternative forms of a gene located at a specific chromosomal location (locus). The alleles of the same gene in the human body differ in their DNA sequence from each other because one is inherited from the mother and one is inherited from the father.

104. In the context of the patents,

> "BRCA2 allele" refers to normal alleles of the BRCA2 locus as well as alleles carrying variations that predispose individuals to develop cancer of many sites including, for example, breast, ovarian and stomach cancer. Such predisposing alleles are also called "BRCA2 susceptibility alleles. '857 Patent, col. 18:8-13.

"BRCA1 allele" refers

> [T]o the double-stranded DNA comprising the locus, allele, or region,

> as well as either of the single-stranded DNAs comprising the locus, allele or region. '857 Patent, col. 19:46-49.

105. I have found nothing in the specification or prosecution history of the '857 Patent that would contradict or alter this definition. This term is used according to its specified definition consistently throughout the patents.

106. I have reviewed the '473 Patent, the '282 Patent, the '999 Patent, the '492 Patent, and the '857 Patent each of which has a claim reciting the term **"nucleotide."** Specifically, this term is recited in claim 1 of the '473 Patent, claims 2, 5-7 of the '282 Patent, claim 1 of the '999 Patent, claim 7 of the '492 Patent, and claim 1 of the '857 Patent.

107. One of skill in the art as of the time of the filing dates of these patents would understand the term "nucleotide" refers to a chemical compound. A nucleotide molecule contains one base together with one sugar and one phosphate. Connecting multiple nucleotides through their phosphate backbone results in a nucleic acid or polynucleotide molecule. *See* Alberts, at 46-47, 60.

108. I have found nothing in the specification or prosecution history of the '473 Patent, the '282 Patent, the '999 Patent, the '492 Patent, and the '857 Patent that would contradict or alter this definition. This term is used according to its specified definition consistently throughout the patents.

109. I have reviewed the '282 Patent, the '492 Patent, and the '857 Patent each of which has a claim reciting the term **"nucleotide/nucleic acid sequence."** Specifically, this is recited in claim 2, 6

and 7 of the '282 Patent, claim 7 of the '492 Patent, and claim 1 of the '857 Patent.

110. One of skill in the art as of the time of the filing dates of these patents would understand the term "nucleotide/nucleic acid sequence" to refer to the order of nucleotides in a nucleic acid molecule. *See* Alberts, at 60. A "nucleotide/nucleic acid sequence" is a convenient abstract representation of the linear structural arrangement of nucleotides in a nucleic acid molecule.

111. In the context of the patents, "nucleotide/nucleic acid sequence" is the specific order in which the nucleotides are arranged in a particular nucleic acid.

The nucleic acids of the present invention will possess a sequence which is either derived from, or substantially similar to a natural BRCA[1/2]-encoding gene or one having substantial homology with a natural BRCA[1/2] encoding gene or a portion thereof. '282 Patent, col. 19:44-48; '492 Patent, col. 18:29-33; and '857 Patent, col. 18:31-35.

112. I have found nothing in the specification or prosecution history of the '282 Patent, the '492 Patent, and the '857 Patent that would contradict or alter this definition. This term is used according to its specified definition consistently throughout the patents.

113. I have reviewed the '282 Patent, the '001 Patent, and the '441 Patent each of which has a claim reciting the term **"method of screening," "method of identifying,"** and **"method of detecting."** Specifically, this is recited in claim 20 of the '282 Patent, claim 1 of the '999 Patent, claim 1

of the '001 Patent, claim 1 of the '441 Patent and claim 1 of the '857 Patent.

114. One of skill in the art as of the time of the filing dates of these patents would use the terms "method for screening," "method of identifying," and "method of detecting" interchangeably, and would understand that they mean any method to survey a large number of subjects to rapidly narrow or pinpoint or identify a specific phenotype or mutation.

115. In the context of the patents:

> The present invention further provides methods of screening the BRCA1 gene to identify mutations. Such methods may further comprise the step of amplifying a portion of the BRCA1 locus, and may further include a step of providing a set of polynucleotides which are primers for amplification of said portion of the BRCA1 locus. The method is useful for identifying mutations for use in either diagnosis of the predisposition to cancer or the diagnosis or prognosis of cancer. The present invention further provides methods of screening suspected BRCA1 mutant alleles to identify mutations in the BRCA1 gene. In addition, the present invention provides methods of screening drugs for cancer therapy to identify suitable drugs for restoring BRCA1 gene product function. '282 Patent, col. 6:59 – col. 7:6; '001 Patent, col. 6:62 – col. 7:9; and '441 Patent, col. 6:64 – col. 7:11.

116. I have found nothing in the specification or prosecution history of the '282 Patent, the '001 Patent, and the '441 Patent that would contradict or alter this definition. This term is used according to its specified definition consistently throughout the patents.

117. I have reviewed the '857 Patent which has a claim reciting the term **"method of diagnosing."** Specifically, this is recited in claim 2 of the '857 Patent.

118. In the field of Human Genetics, one of skill in the art as of the time of the filing dates of these patents would understand that the term "method for diagnosing" commonly included determining whether or not the patient has a genetic alteration.

119. In the context of the patents, "methods for diagnosing"

[A]re applicable to any tumor in which BRCA2 has a role in tumorigenesis. The diagnostic method of the present invention is useful for clinicians, so they can decide upon an appropriate course of treatment. '857 Patent, col. 15:9-13.

The probes and primers based on the BRCA2 gene sequences disclosed herein are used to identify homologous BRCA2 gene sequences and proteins in other species. These BRCA2 gene sequences and proteins are used in the diagnostic/prognostic, therapeutic and drug screening methods described herein for the species from which they have been isolated." '857 Patent, col. 26:57-63.

120. I have found nothing in the specification or prosecution history of the '857 Patent that would contradict or alter this definition. This term is used

according to their specified definition consistently throughout the patents.

121. I have reviewed the '282 Patent , the '999 Patent , the '001 Patent , the '441 Patent and the '857 Patent each of which has a claim reciting the term **"gene."** Specifically, this is recited in claim 20 of the '282 Patent , claim 1 of the '999 Patent , claim 1 of the '001 Patent , claim 1 of the '441 Patent and claim 2 of the '857 Patent.

122. One of skill in the art as of the time of the filing dates of these patents would define "gene" as aggregates of segments of the chromosome. This individual would also understand that a "gene" did not necessarily encode a single protein, but may encode multiple isoforms due to alternative splicing, or does not encode a protein at all.

123. In the context of the patents, the

> "BRCA2 Locus," "*BRCA2 Gene*," "BRCA2 Nucleic Acids" or "BRCA2 Polynucleotide" each refer to polynucleotides, all of which are in the BRCA2 region, that are likely to be expressed in normal tissue, certain alleles of which predispose an individual to develop breast, ovarian and stomach cancers. Mutations at the BRCA2 locus may be involved in the initiation and/or progression of other types of tumors. The locus is indicated in part by mutations that predispose individuals to develop cancer. These mutations fall within the BRCA2 region described *infra*. The BRCA2 locus is intended to

include coding sequences, intervening sequences and regulatory elements controlling transcription and/or translation. The BRCA2 locus is intended to include all allelic variations of the DNA sequence. These terms, when applied to a nucleic acid, refer to a nucleic acid which encodes a BRCA2 polypeptide, fragment, homolog or variant, including, *e.g.*, protein fusions or deletions. The nucleic acids of the present invention will possess a sequence which is either derived from, or substantially similar to a natural BRCA2-encoding gene or one having substantial homology with a natural BRCA2 encoding gene or a portion thereof. The coding sequence for a BRCA2 polypeptide is shown in SEQ ID NO:1 and FIG. 3, with the amino acid sequence shown in SEQ ID NO:2." '857 Patent, col. 18:8-37.

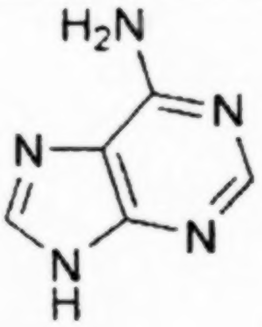
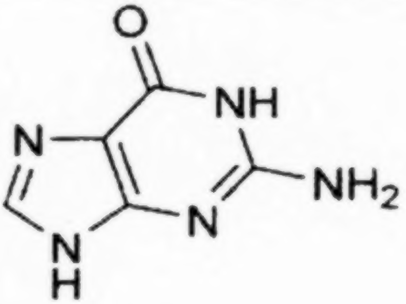
124. I have found nothing in the specification or prosecution history of the '282 Patent, the '999 Patent , the '001 Patent , the '441 Patent and the '857 Patent that would contradict or alter this definition. This term is used according to its specified definition consistently throughout the patents.

III. DNA IS A CHEMICAL COMPOUND

125. DNA, which stands for deoxyribonucleic acid, is a type of chemical compound called a nucleic acid. At its most basic level, a DNA molecule is composed

of several chemical elements, namely Carbon, Hydrogen, Oxygen, Nitrogen, and Phosphorus. These chemical elements make up repeating units that are connected to form a strand or polymer of the DNA molecule. These repeating units of DNA are known as nucleotides. The standard nucleotides in vertebrate DNA contain four different bases: Adenine, Thymine, Cytosine, and Guanine. These bases are linked together by chemical bonds via a sugar-phosphate backbone. As shorthand for convenience, scientists often denote nucleotides by the first letter of the names of their bases: "A" for Adenine; "G" for Guanine; "T" for Thymine; and "C" for Cytosine. Presented below in Figure 1[1] are depictions of the chemical structures of the four nucleotides Adenine, Guanine, Thymine, and Cytosine.

Fig. 1

	
Adenine	Guanine

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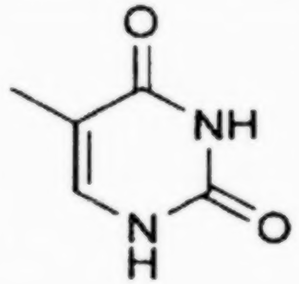
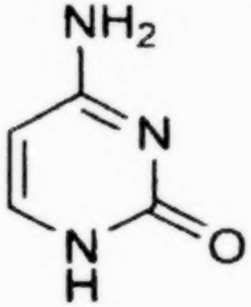
[1] Figure 1 is modified from the online source Wikipedia.com.

	
Thymine	Cytosine

126. A molecule of DNA is typically represented by the linear order of its nucleotides, *i.e.*, its "nucleotide sequence" or simply – its "sequence." A nucleotide sequence is not merely information or letters of the English alphabet – the nucleotide sequence defines the structure and chemical properties of a particular DNA molecule based on the linear order of nucleotides in that particular DNA molecule. The structure and chemical properties of a particular DNA molecule can thus determine its function.

127. Indeed, the letters of the alphabet are often used to name most chemical compounds, not just DNA. For example, the substance commonly known as water is often represented by its chemical formula, H_2O. This chemical formula not only tells a scientist that the chemical substance in question is water, but it also provides other important information about its chemical, structural, physical, and thus, its functional properties. The scientist could readily deduce, for example, that one molecule of water is made up of two atoms of Hydrogen and one atom of Oxygen that are bonded together, and that the structure of an individual water molecule tells a chemist how many water molecules interact with

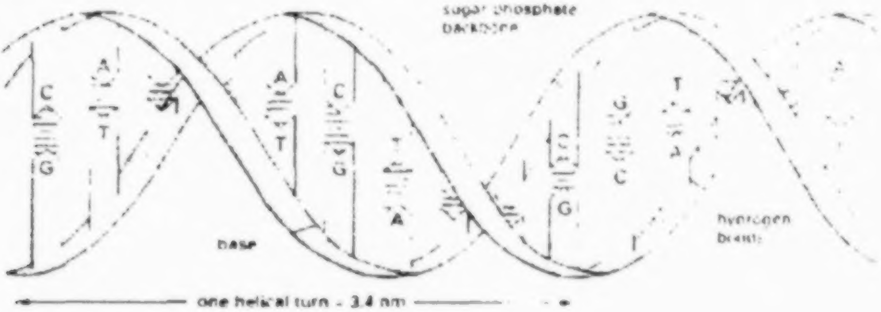
each other and thereby form, *e.g.*, an ice crystal. Accordingly, the scientific notation of any chemical compound provides information about that chemical compound, such as its chemical, structural, and physical properties. These very properties can thus determine the compound's function. Likewise, the physical, structural, and chemical properties of a DNA molecule determine its function. Treating DNA as purely informational is inaccurate.

128. Various molecules can, through chemical reactions and physical interactions, transmit information. Adrenaline (also known as Epinephrine), for example, is secreted by the adrenal gland of the body in response to a stressful situation. Once secreted, adrenaline increases the strength and rate of the heartbeat and raises the blood pressure to prepare the body to react to the stressful situation. This cascade of events is a transmission of information—from one part of the body to another. On a molecular level, however, this cascade is caused by adrenaline's chemical composition and structure, which allow adrenaline to bind to certain cells throughout the body thereby conveying the message that certain metabolic effects are desired. Thus, adrenaline is an information carrier whose information is conveyed through its chemical structure.

129. Generally, DNA exists as a double helix, which consists of two intertwined strands of DNA. This structure is made possible because each base in one strand is paired via hydrogen bonds with another base in the other, complementary strand (Adenine

pairs with Thymine and Cytosine pairs with Guanine). Figure 2[2] depicts the structure of the double-helix and the complementary pairing of the four bases, represented by A, T, C, and G.

Fig. 2


sugar phosphate backbone
C
G
A
T
A
T
C
G
T
A
G
C
T
A
base
hydrogen bonds
one helical turn = 3.4 nm

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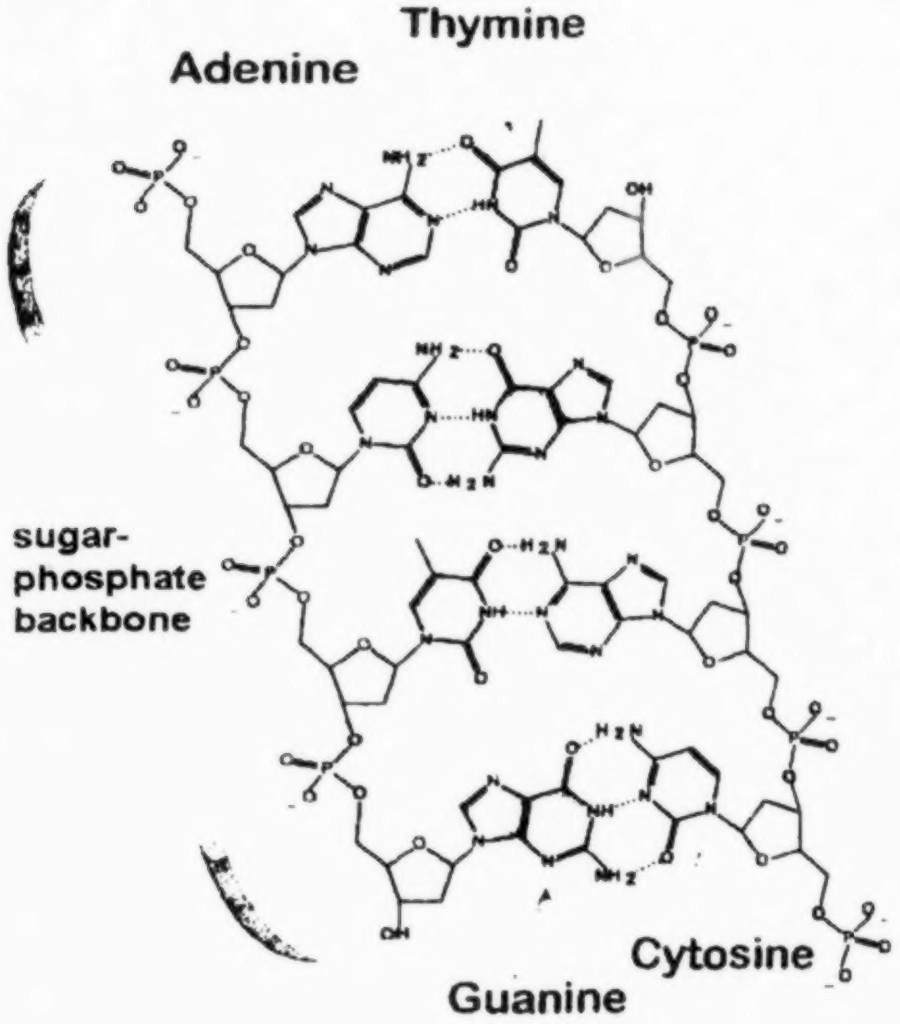
[2] Figure 2 is modified from a figure at page 101 of Alberts.

130. Figure 3[3] illustrates the chemical bonding between the bases and the sugar-phosphate backbone of the double helix structure.

Fig. 3


Thymine
Adenine
sugar-
phosphate
backbone
Cytosine
Guanine

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[3] Figure 3 is modified from the entry for "DNA" at the online source Wikipedia.com.

IV. NATIVE DNA HAS DIFFERENT PROPERTIES AND FUNCTIONS FROM ISOLATED DNA

131. DNA as it is found in the human body, *i.e.*, native DNA, is one integral component of chromosomes. Chromosomes are complex structures that carry genes and which are located in most cells of the human body. Proteins represent another integral component of chromosomes. These proteins are bound to the DNA molecules in the chromosomes and modulate the structure and function of the DNA molecules to which they are bound. Thus, native DNA is never found floating freely in cells of the body, but is packaged along with proteins to form chromosomes. Figure 4[4] below is a schematic drawing of the many levels of packaging of DNA and proteins in a chromosome structure.

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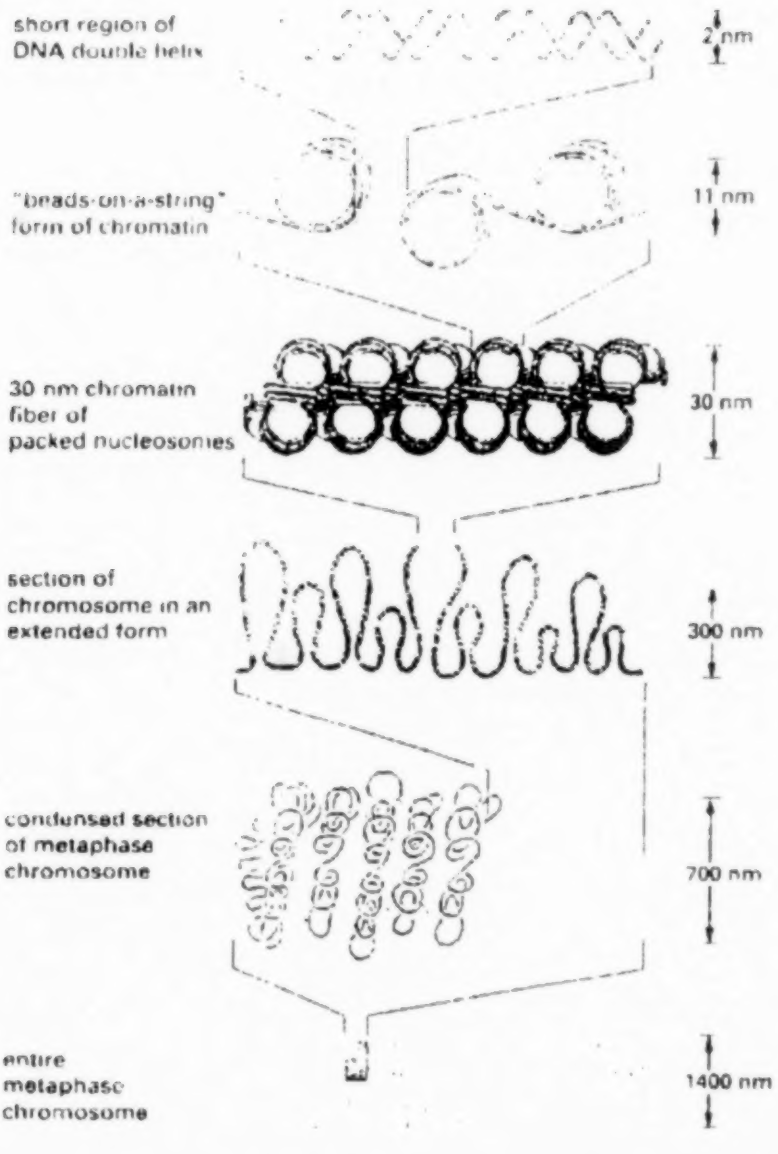
[4] Figure 4 is modified from Figure 8-30 of Alberts.

Fig. 4


short region of DNA double helix
2 nm
"beads-on-a-string" form of chromatin
11 nm
30 nm chromatin fiber of packed nucleosomes
30 nm
section of chromosome in an extended form
300 nm
condensed section of metaphase chromosome
700 nm
entire metaphase chromosome
1400 nm

132. The dynamic interaction between chromosomal proteins and native DNA in the body has a major role in establishing which genes are active and which are inactive and the level of their activity. In addition, the chromosomal proteins mediate the interplay between the native DNA and the rest of the cell. Moreover, chemical modifications

of the DNA molecule, *e.g.*, methylation, can have a major impact on the function of the DNA molecule in the body. Accordingly, there are many factors in the cell, so-called epigenetic factors, which can influence native DNA and consequently the presentation of a trait.

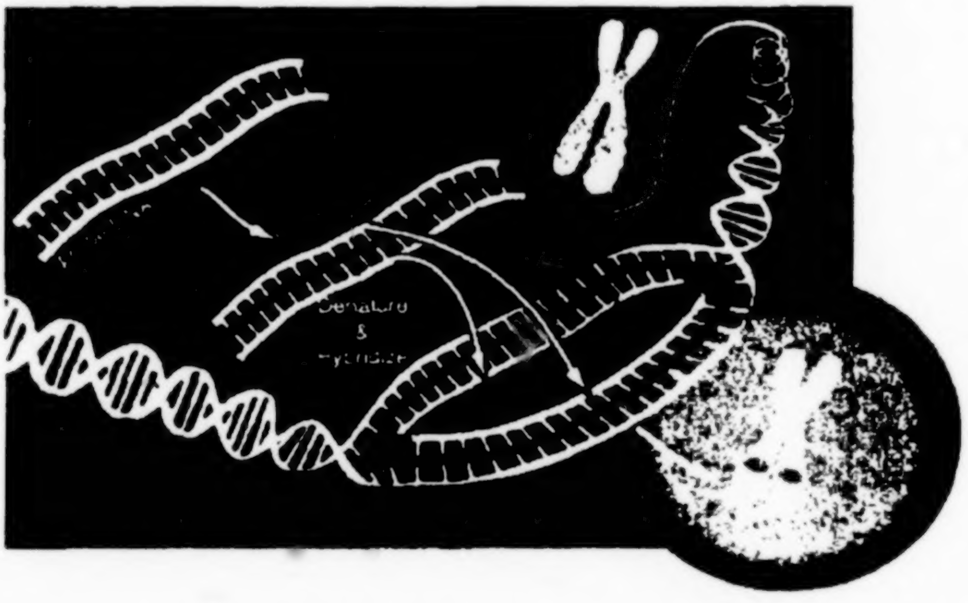
133. To isolate DNA molecules from the body, the entire genome must be extracted from tissues or cells of the body and the chromosomal proteins must be removed. To isolate a specific gene of interest, the relevant DNA fragment must be excised from the genome. The dynamic chemical, physical, and functional interaction between DNA and chromosomal proteins is therefore eliminated from an isolated DNA molecule.

134. Once a DNA molecule is isolated, it gains new properties which, in its native state, it did not possess. These functions make isolated DNA molecules useful as tools for many biotechnological applications such as, for example, diagnostic assays to identify and detect potentially lethal human genetic alterations, and to identify drugs that might be able to cure cancer.

135. One example is the use of isolated DNA molecules as probes. A probe can be a fragment of a DNA molecule of variable length (usually 100-1000 bases long), which is used to detect the presence of a specific target DNA molecule in a sample. The probe is designed to bind specifically to the target DNA molecule of interest based on the nucleotide sequence of the target DNA. The sequence of bases in the probe determines the sequence of bases in the target to which the probe can bind because Adenine always binds to Thymine and Guanine to Cytosine. This

pairing between the probe and its complementary target DNA is called hybridization. To detect hybridization of the probe to its target sequence, the probe is labeled with a detectable, *e.g.*, fluorescent or radioactive, marker. Figure 5[5] below illustrates how an isolated DNA molecule can serve as a probe to target a specific region in the native DNA located within a chromosome.

Fig. 5



136. Isolated DNA molecules can also be used as primers for sequencing reactions. As with probes, primers that are complementary to an exact location of a much larger target DNA molecule can be designed to initiate a sequencing reaction at that location. A scientist can use the probe to analyze the

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[5] Figure 5 is modified from a figure at the website of the Mount Sinai Hospital (http://www.mountsinai.on.ca/care/pdmg/genetics/chromosomes).

native DNA molecule. Native DNA, in contrast, cannot be used as a primer or a probe.

137. The isolated DNAs are excised, extracted or synthetic chemical compounds made by the hands of molecular biologist, not by nature. They are structurally distinct from any substance found in the human body—indeed, in all of nature.

138. Isolated DNA is different in kind, not merely different in degree of purity, from any composition found in nature. Isolated DNA acquires new properties not shared by its native counterpart. These new properties impart the isolated DNA molecules with new characteristics and new utilities. Unlike native DNA, the isolated form can be used as a probe, a diagnostic tool that a molecular biologist uses to target and bind to a particular portion of DNA, allowing it to be detectable using laboratory machinery. Native DNA cannot be used this way. Isolated DNA can also be used as another diagnostic tool, a "primer," which is used in "sequencing" DNA, a method used by a molecular biologist to determine the primary structure of a DNA molecule. In sequencing, a primer binds to, or "hybridizes" with, a DNA target, such as a BRCA1/2 gene, DNA, or a synthetic DNA complementary to mRNA ("cDNA") to form a hybridization product that acts as a substrate for the enzymes used in the sequencing reaction.

139. Native DNA does not have the chemical, structural, functional properties that make isolated DNA so useful to the molecular biologist. Native DNA cannot be used as molecular tools, such as probes and primers, and cannot be used to detect mutations. Nor can it be used in sequencing reactions to determine the structure of a DNA

molecule. Excision, extraction, and purification from cellular components, or synthesizing DNA directly from its nucleotide components, is essential to be able to use the isolated DNA molecules as primers or probes. Thus, only isolated DNA molecules have the required chemical, structural and functional properties important for use as diagnostic tools and in the claimed diagnostic methods.

140. RNA cannot be used as a sequencing primer, because its chemistry is incompatible with performing as a sequencing primer.

141. Dr. Sulston's statement that "[t]he physical form in which [genetic sequences] occur is unimportant; what matters is the *informational content*" is thus inaccurate (*see* D. Sulston, ¶15). To the contrary, the physical form of a DNA molecule can significantly impact its function and the information it can yield.

V. GENES ARE INEXTRICABLY LINKED TO OTHER COMPONENTS IN THE HUMAN BODY

142. In the human body, genes are located on chromosomes. Historically, the term "gene" has been used to describe the unit that is responsible for the inheritance of a discrete trait, such as the color of peas in a peapod. In molecular terms, a gene is an aggregate of several segments of a chromosome. Some segments regulate the activity of the gene. From other segments, various types of RNA are produced. Types of RNA include tRNA, rRNA, and mRNA. From an mRNA template, protein is typically produced. In addition, the segments that

make up one gene can be physically located adjacent to each other or apart on the chromosome.

143. The body does not have a mechanism "for isolating" genes, contrary what Dr. Jackson contends (*see* Jackson, ¶29). In the body, native DNA remains associated with chromosomes. Moreover, genes are also not like "mathematical algorithms" as Dr. Jackson proclaims (*see* D. Jackson, ¶47). This is because genes are *physical* entities, the functions of which are inextricably linked to their chemical composition and their interaction with other cellular components. Besides, the patents at issue in this case define an "isolated" nucleic acid as "substantially separated from other cellular components." '473 Patent, col. 19:8-9.

144. In the human body, the 23 pairs of chromosomes are located in a cellular structure called the nucleus. Mitochondria, other cellular structures that convert food into energy, also contain a chromosome. A small fraction of human genes are carried by this mitochondrial chromosome. In humans, mitochondrial genes are maternally inherited because the mitochondria of an embryo are supplied by the egg but not by the sperm cell.

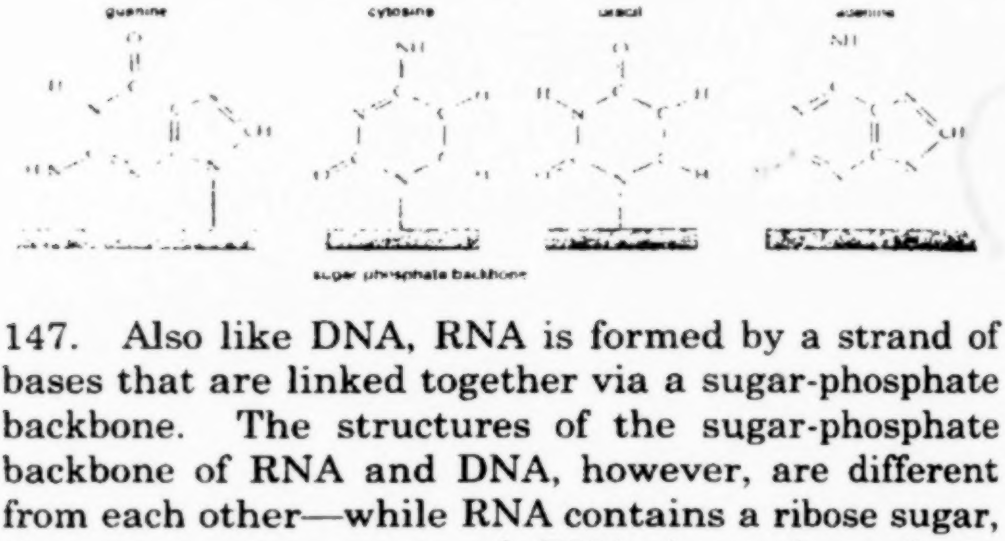
145. Cells divide throughout a person's life. The chromosomes, and with them genes and the DNA of which they are comprised, are also duplicated. The process of cell division takes place in the germline to generate egg and sperm cells. Cell division also takes place in the remaining, so-called somatic, cells of the body.

VI. RNA IS STRUCTURALLY AND FUNCTIONALLY DISTINCT FROM DNA

146. Like DNA, RNA – which stands for ribonucleic acid – is a chemical compound. Unlike DNA, however, the four bases that make up RNA are Guanine, Cytosine, *Uracil*, and Adenine. Thus, instead of the base Thymine, RNA contains Uracil. Common abbreviations of the bases of RNA are: "G" for guanine; "C" for Cytosine, "U" for Uracil, and "A" for Adenine. Each base together with one sugar and one phosphate molecule makes up one repeating unit known as a nucleotide of the RNA. Figure 6[6] below provides an illustration of the chemical structures of the four chemical bases of RNA.

Fig. 6

FOUR BASES OF RNA



147. Also like DNA, RNA is formed by a strand of bases that are linked together via a sugar-phosphate backbone. The structures of the sugar-phosphate backbone of RNA and DNA, however, are different from each other—while RNA contains a ribose sugar, the sugar component of DNA is a deoxyribose.

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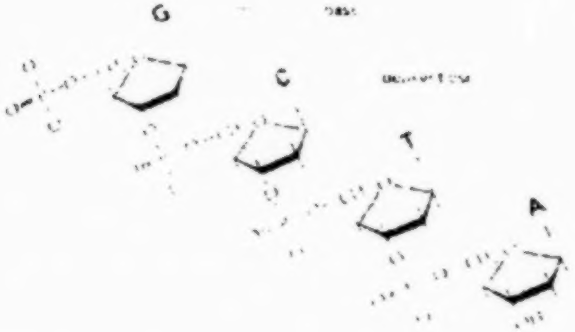
[6] Figure 6 is modified from a figure at page 100 of Alberts.

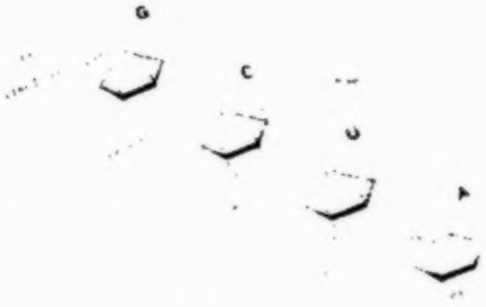
Figure 7[7] below is a depiction of the four bases of DNA and RNA, respectively, linked by a sugar-phosphate backbone.

Fig. 7

SUGAR-PHOSPHATE BACKBONE OF DNA



SUGAR-PHOSPHATE BACKBONE OF RNA



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[7] Figure 7 is modified from a figure at pages 100 and 101 of Alberts.

148. The different structures of RNA and DNA affect their respective properties and functions. For example, unlike native DNA, which forms a double helix, RNA usually exists as a single strand. Like DNA in a cell, RNA is typically not found floating freely in solution. Cellular RNA is always bound to proteins. Further, DNA is a very stable molecule—DNA has been recovered from millennia-old fossils—whereas RNA, on the other hand, is much less stable. Even in the cell, RNA is sometimes degraded within hours of its generation. This difference in stability is one reason why isolated DNA molecules are more suitable for many biotechnology and diagnostic applications. Figure 8[8] below is an illustration of a single-stranded molecule of RNA.

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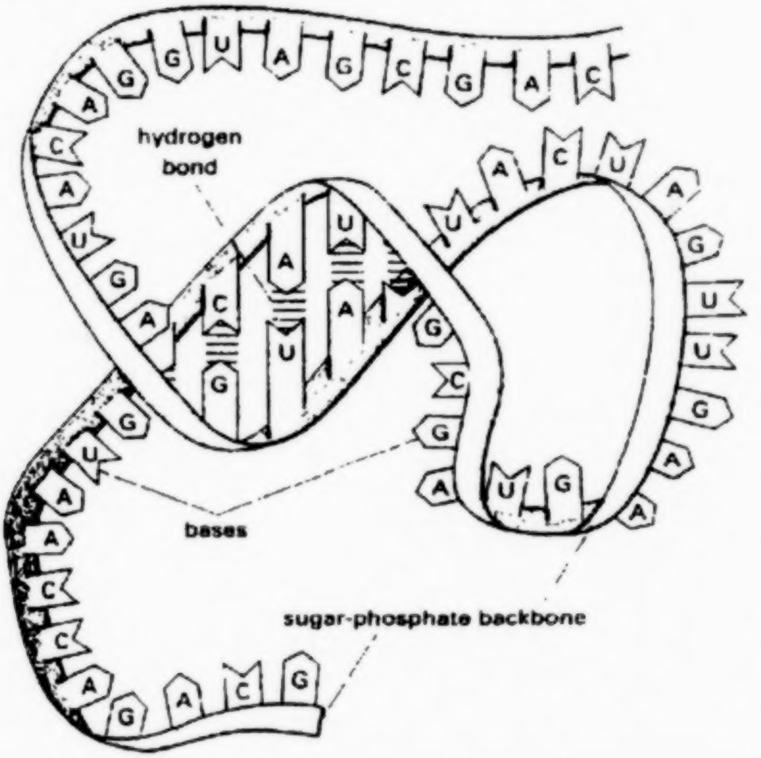
[8] Figure 8 is modified from a figure at page 100 of Alberts.

Fig. 8

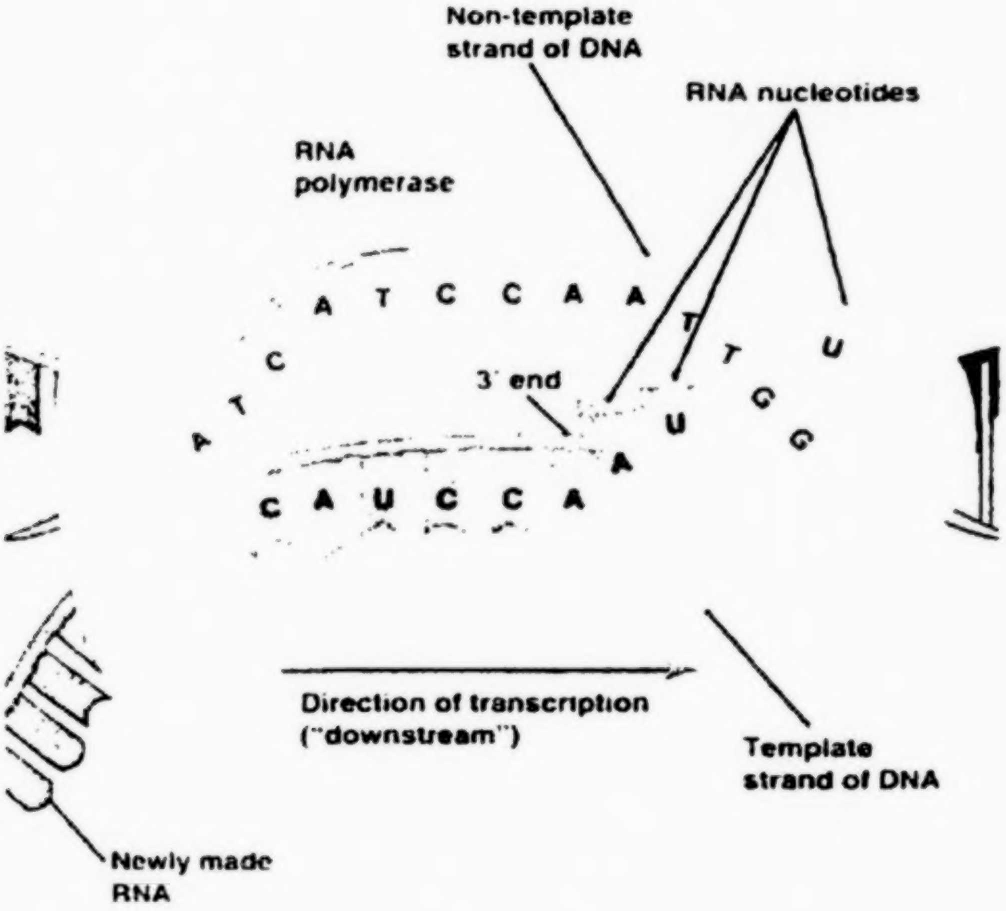


149. The process of RNA generation is called "transcription." Many different RNA molecules are transcribed and processed from the native DNA of a chromosome. The regulation of RNA transcription involves chromosomal segments that are usually not themselves transcribed into RNA. In fact, regulatory sequences can be at a very different location on the chromosome. These regulatory regions together with the region that is transcribed into RNA form a gene.

150. During transcription of RNA from DNA, a discrete segment of the DNA unwinds and the bases of the DNA molecule act as "clamps" that hold the bases of the newly forming RNA in place while the chemical bonds of the sugar-phosphate backbone are formed. This process is mediated by a structure in

the cell known as the RNA polymerase. Adenine binds to Uracil, Thymine to Adenine, Guanine to Cytosine, and Cytosine to Guanine. Figure 9[9] below is an illustration of the process of RNA transcription from a DNA template strand.

Fig. 9


Non-template strand of DNA
RNA nucleotides
RNA polymerase
A T C C A A
C
T
A
T
T
U
3' end
G
U
G
A
C A U C C A
Direction of transcription ("downstream")
Template strand of DNA
Newly made RNA

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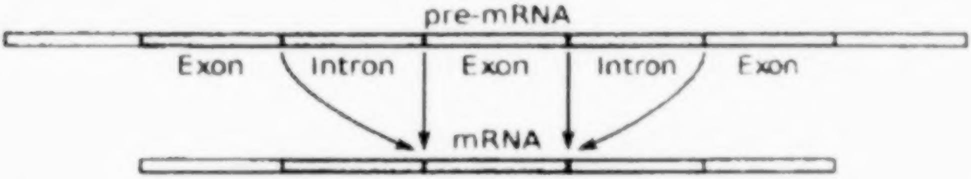
[9] Figure 9 is modified from a figure at the website of the Department of Biology of the University of Miami (http://www.bio.miami.edu/~cmallery/150/gene/c7.17.7b.transcription.jpg).

151. A single gene may give rise to various different RNA molecules, which in turn may give rise to various different proteins. A newly transcribed RNA molecule (a "transcript"), or precursor messenger RNA ("pre-mRNA"), is processed to result in a mature messenger RNA ("mRNA"). Pre-mRNA contains nucleotides that are eliminated during a process called "splicing." The segments of the pre-mRNA that spliced out are called introns (which can contain regulatory sequences), while the remaining segments, called exons, are ligated together. In addition, a chemical "cap" is added to one end of the RNA. A "tail" of nucleotides that contain the base adenine is added to the other end. The final mRNA molecule contains only exons, a cap, and a poly-adenine tail. Figure 10[10] below is a simplified illustration of the process of pre-mRNA splicing to form mature mRNA.

Fig. 10



152. In addition, during a process called "alternative splicing," different combinations of exons from the same pre-mRNA molecule can be spliced together yielding alternative mRNA products.

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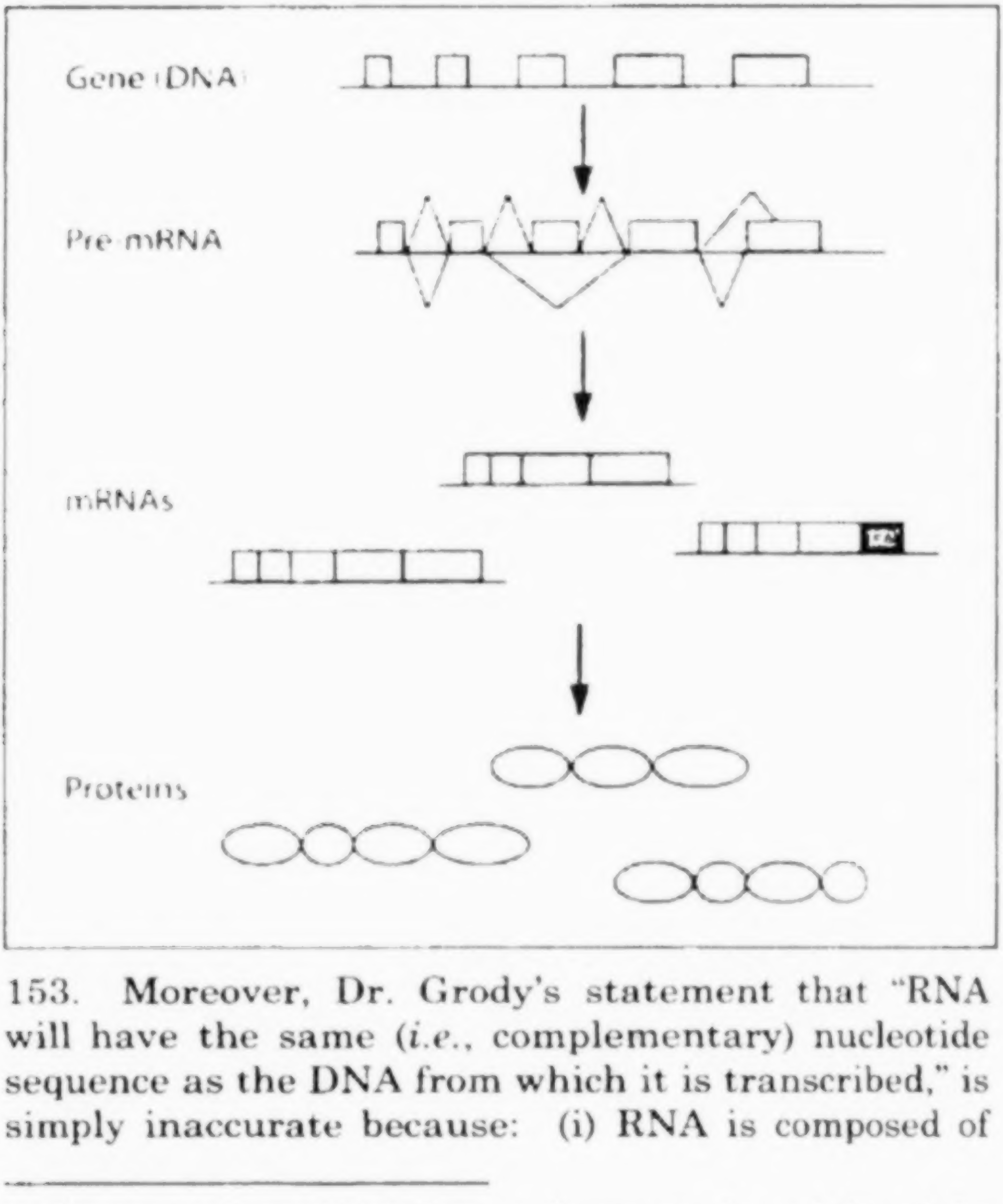
[10] Figure 10 is modified from the entry for "intron" at the online source Wikipedia.com.

Figure 11[11] is an schematic drawing of the process of alternative splicing.

Fig. 11



153. Moreover, Dr. Grody's statement that "RNA will have the same (*i.e.*, complementary) nucleotide sequence as the DNA from which it is transcribed," is simply inaccurate because: (i) RNA is composed of

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[11] Figure 11 is modified from a figure at the website of the Scottish Crop Research Institute (http://www.scri.ac.uk/scri/image/Research/genetics/genesanddevelopment/RNA_fig1.jpg).

different bases; (ii) the nucleotides in the RNA bind to the nucleotides in the DNA—they are not the same; and (iii) the RNA nucleotide sequence is modified by splicing, and adding of a cap and a tail of adenine. *See* D. Grody, ¶52.

154. Thus, contrary to Dr. Leonard's statement that "the coding effect of a cDNA is the same as that of the original DNA from which it was originally derived despite having a shorter sequence," alternative splicing can give rise to many different mRNAs from the same native DNA molecule (*see* Leonard, ¶75). cDNAs can be prepared from mRNAs as discussed below. However, the cDNA captures that one mRNA from which it was synthesized and not all other splice variants that result from that one gene.

VII. PROTEINS ARE TRANSLATED FROM RNA

155. Proteins are generally large, complex molecules that play many critical roles in the body. They do most of the "work" in the body and are required for the structure, function, and regulation of the body's tissues and organs.

156. Proteins are made up of hundreds or thousands of smaller units called amino acids, which are attached to one another in long chains. There are 20 different types of amino acids that can be combined to make a protein. The sequence of amino acids determines each protein's unique 3-dimensional structure and its specific function.

157. Proteins are translated from mRNA through a process called "translation." During translation, mRNA serves as a template to assemble a protein.

Three consecutive bases in an mRNA molecule constitute a "codon," which codes for one of the 20 amino acids. Pairing interactions take place between an mRNA molecule and another RNA molecule known as tRNA, which serves as an adaptor during protein translation. Specifically, sets of three nucleotides in the coding region of an mRNA, react with three nucleotides in a tRNA in such a way as to cause the amino acid linked to the tRNA molecule to be chemically transferred to the growing polypeptide chain destined to become a protein. The bases of the mRNA serve as "clamps" to hold the amino acids in place while the chemical bonds between the individual amino acids are formed. During translation, the mRNA template, the tRNA, the newly forming polypeptide chain, and the next amino acid reside in a multi-protein complex named ribosome. Once a protein is translated in typically undergoes post-translational modifications that are important for the protein's function. Figure 12[12] below provides an illustration of the process of protein translation.

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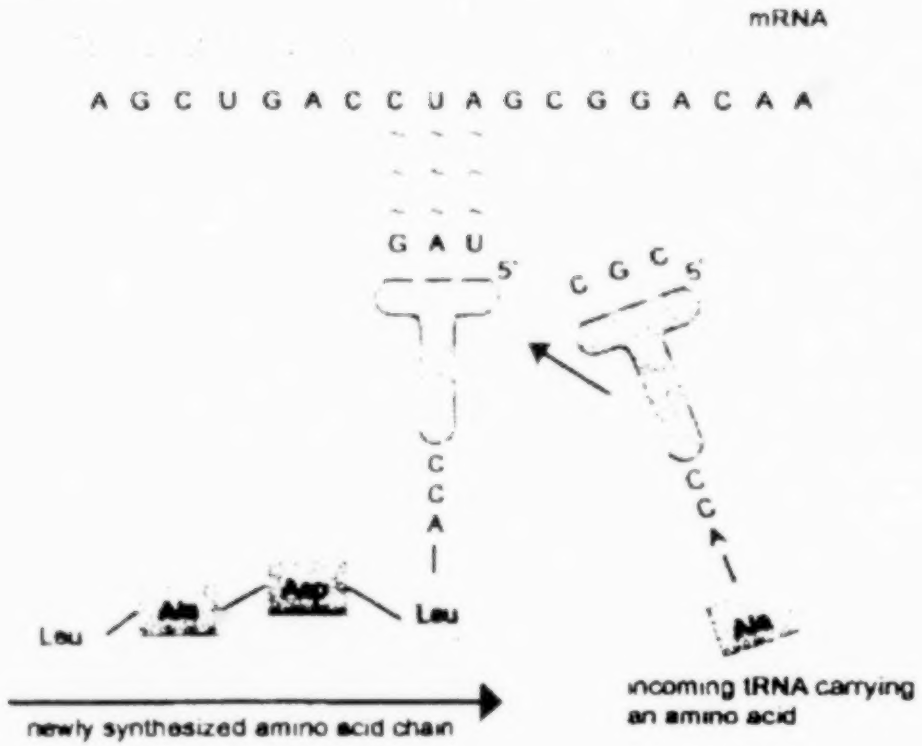
[12] Figure 12 is modified from a figure at the website of the Genome Engineering Laboratory of the Institute for Bioinformatics at the National Yang Ming University, Taiwan (http://gel.ym.edu.tw/~ycl6/sc2005/images/translation.gif).

Fig. 12


mRNA
A G C U G A C C U A G C G G A C A A
G A U
5'
C G C
5'
C
C
A
C
C
A
Leu
Ala
Asp
Leu
Ala
newly synthesized amino acid chain
incoming tRNA carrying an amino acid

158. The genetic code describes which codons code for which amino acids. For example, the codon Adenine-Thymine-Guanine encodes the amino acid Methionine. Thus, the chemical composition of an mRNA molecule determines the amino acid composition of a protein.

159. The genetic code is very much dependent on the cellular environment. For example, the three nucleotides Uracil-Guanine-Adenine do not encode an amino acid in the cytoplasm of a typical cell but it stops the process of translation so that the polypeptide is no further extended. In mitochondria, however, the same codon encodes the amino acid Tryptophane.

160. I note that in his declaration, Dr. Sulston states that "it wasn't until 1953—the year of the discovery of the structure of DNA—that we came to understand how DNA played its role." D. Sulston, ¶13. I disagree. While the DNA double helix was originally suggested in 1953 by James D. Watson and Francis Crick, the genetic code was not elucidated until the early 1960's. The physical structure of the DNA molecule by itself does not reveal how the DNA molecule functions. In fact, even knowing the nucleotide sequence by itself does not tell function.

VIII. cDNA, RNA, AND NATIVE DNA ARE STRUCTURALLY AND FUNCTIONALLY DIFFERENT FROM EACH OTHER

161. Complementary DNA, or "cDNA," is commonly synthesized from a mature mRNA in a reaction catalyzed by a protein known as reverse transcriptase. cDNA received its name because each base in the cDNA can bind to a base in the mRNA from which the cDNA is synthesized. In other words, it is "complementary" to the mRNA from which it is synthesized.

162. cDNA, as other isolated DNA molecules that are extracted, excised or synthesized, can be a useful tool for researchers as primers and probes in biotechnological and diagnostic applications. In the real world, virtually only synthetic DNA is used as primers and probes.

163. Moreover, when a scientist wants to express a specific protein in a cell that does not normally express that protein to learn more about the protein, the scientist can transfer the cDNA that codes for the protein to a recipient cell. If the cDNA is operatively

linked to a promoter that initiates transcription from the cDNA, the recipient cell will then express the protein of interest.

164. An isolated cDNA molecule is an artificial construct that does not exist in the body and hence is structurally and functionally different from both native DNA and RNA.

165. The method of cDNA construction helps to understand its multiple structural and functional differences from both native DNA and RNA. Several steps are required to construct a cDNA, involving many elegant molecular biology techniques. First, mature RNA is isolated from the tissues or cells of an organism. cDNA is then synthesized from the mature RNA using reverse transcriptase. In this process, the bases of the RNA serve as clamps while the chemical bonds between the nucleotides of the newly forming cDNA strand are formed. Uracil binds to and thereby acts as a clamp for Adenine, Thymine for Adenine, Guanine for Cytosine, and Cytosine for Guanine.

166. The synthesis of cDNA from very long mRNA molecules, such as *BRCA1* and *BRCA2*, often does not result in a cDNA strand that is as long as the mRNA chain. Instead, not unlike a puzzle, several cDNA fragments have to be pieced together to arrive at a composite full length cDNA. Initially, the cDNA is single stranded but the second strand can be synthesized to form a double stranded cDNA molecule.

167. Contrary to Dr. Mason's statement that "cDNA is simply a mirror of the RNA" and that "the functional sequence of the cDNA is identical to the

functional sequence of the DNA," cDNA is both structurally and functionally different from RNA and from native DNA. cDNA is not mirror of mRNA nor is it identical to native DNA found in the body. *See* Mason, ¶29.

168. cDNA is *structurally* different from native DNA. First, cDNA made from an mRNA does not contain introns in contrast to native DNA, which contains many intronic sequences. Second, cDNA can contain sequences that correspond to the poly-adenine tail of mRNA, which does not exist in native DNA. Third, because it is not associated with proteins as with native DNA and because it lacks a 5' cap, no protein can be produced from an isolated cDNA molecule without introduction of regulatory sequences. Fourth, the sugar-phosphate backbone of native DNA is usually chemically modified, *e.g.*, by methylation. In contrast, the sugar-phosphate backbone of cDNA is not modified. Finally, as discussed above, isolated cDNA can serve as a probe, as a target for a probe, and as a template for a polymerase chain reaction ("PCR"), all of which native mRNA cannot do.

169. cDNA is also *functionally* different from native DNA. First, native DNA contains regulatory sequences. These regulatory sequences are not present in cDNA because they are not present in the mRNA from which the cDNA was synthesized. Second, because cDNA does not contain intronic sequences, mRNA can be transcribed from cDNA without the need for splicing. Third, introducing a cDNA alone into a cell does not give rise to protein production from that cDNA. Fourth, native DNA and chromosomal proteins form a functional unit;

isolated or synthetic cDNA, however, is not associated with chromosomal protein and can thus be used as a molecular tool in various biotechnological applications.

170. As with native DNA, cDNA is *structurally* different from RNA, both pre-mRNA and mature mRNA. First, the set of bases in DNA is different from the set of bases in RNA. While the four bases in DNA are Adenine, Cytosine, Guanine, and Thymine, the four bases in RNA are Uracil, Adenine, Cytosine, and Guanine. Second, the sugar-phosphate backbone in DNA is chemically different from the sugar-phosphate backbone of RNA. This difference in structure allows DNA to form the famous double helix.

171. cDNA is also *functionally* different from mRNA. First, cDNA is a much more stable molecule than mRNA. Second, protein can be translated directly from mRNA whereas protein cannot be directly translated from cDNA but requires the additional step of RNA transcription. Third, in the body, tens of thousands different mRNA molecules are present. Synthesized cDNA, on the other hand, is generated in the laboratory commonly as a homogenous population of molecules of the same kind to study the properties and functions of a specific gene of interest.

172. In addition to being structurally and functionally different from each other, native DNA and mRNA convey less information to researchers, as opposed to isolated DNA molecule such as cDNA. In its native state, the sequence of DNA or RNA molecule is almost like a mystery – they convey little or no information regarding their biological or

clinical significance. Only upon isolation, synthesis, and complex analysis can this information become available to researchers and clinicians. Thus, isolated DNA is very much *informationally* different in kind.

IX. ISOLATED *BRCA1* AND *BRACA2* cDNAS ARE SYNTHETIC, MAN-MADE COMPOSITIONS THAT ARE STRUCTURALLY AND FUNCTIONALLY DIFFERENT FROM NATIVE *BRCA1* AND *BRACA2* RNA AND DNA

173. Isolated DNAs are structurally and functionally distinct from any DNA found in nature. The isolated *BRCA1* and *BRCA2* DNA molecules claimed in the *BRCA1* and *BRCA2* patents are likewise extracted, purified, or synthetic, and are structurally distinct from any substance found in the human body, or elsewhere in nature. For example, native DNAs are physically connected to DNA regulatory sequences and proteins that determine which DNA sequences are expressed, how and where they expressed, and their level of expression. In contrast, the claimed isolated *BRCA1* and *BRCA2* DNAs are not associated with these regulators and do not contain this information.

174. As with isolated cDNA molecules described above, isolated *BRCA1* and *BRCA2* DNA molecules are typically man-made, synthetic molecules. They are structurally distinct from any substance found in the human body, or anywhere else in nature. Based on these structural differences, isolated *BRCA1* and *BRCA2* DNA molecules have very different functions and uses than native *BRCA1* and *BRCA2* RNA and

DNA molecules. For example, isolated *BRCA1* and *BRCA2* DNA molecules can function as diagnostic probes and primers for detecting mutations, whereas native *BRCA1* and *BRCA2* RNA and DNA molecules cannot. Likewise, native *BRCA1* and *BRCA2* DNA molecules can pass genes from generation to generation, whereas isolated *BRCA1* and *BRCA2* DNA molecules cannot.

175. With regard to real world practical functions, isolated *BRCA1* and *BRCA2* DNA molecules can be used as primers for DNA sequencing to determine the chemical structure of a patient's *BRCA1* and *BRCA2* DNA sequence, respectively—native genes or DNA in a chromosome cannot be used for these functions.

176. Dr. Sulston states in his declaration that "[g]enetic sequencing is the process by which one 'reads,' or determines, the ordering of the 4 letters (A, T, C, and G) within a specified part of the genome." D. Sulston, ¶ 20. However, sequencing is not simply "reading" a series of letters through a microscope. A DNA sequence cannot be determined by mere inspection. Instead, a series of extractions and chemical reactions must be performed.

177. In order to initiate a DNA sequencing reaction, at least part of the sequence of the target DNA molecule must be known. Plaintiffs fail to appreciate that sequencing of the *BRCA1* and *BRCA2* genes today is based on the breakthrough inventions that led to the patents at issue in this case, *i.e.*, the elucidation of the chemical structure of the genes and their association with an increased risk in breast and ovarian cancer.

178. To determine a DNA sequence of a patient for diagnostic purposes, a biological sample, such as a blood sample, from the patient must be processed. Native DNA or mRNA must be purified from the patient sample. The purification of native DNA of the entire genome, however, does not result in the purification of a single gene. Given that the DNA sequence of the human genome is over three billion nucleotides long, this initial purification step is still a long way from obtaining the sequence of a specific gene. To put things in perspective, the size of the *BRCA1* cDNA relates to the size of the entire genome approximately as a grain of sand to the height of the observation floor of the Empire State Building.[13]

179. Similarly, purification of mRNA from a patient sample yields a mixture of thousands or tens of thousands of different mRNA molecules. Even if cDNA is synthesized from this pool of mRNA molecules, the resulting cDNA molecules are similarly a mixture of thousands or tens of thousands of different cDNAs.

180. The standard method for sequencing DNA commonly used at the filing date of the patents was called the dideoxy sequencing method. Site-specific sequencing, as opposed to full length sequencing, is often used to identify an alteration at a specific nucleotide position.

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[13] For this analogy, I have used the following numbers: diameter of a grain of sand—0.6mm; height of the observation floor of the Empire State Building—320m; length of the cDNA of BRCA1 in the '473 patent (SEQ ID NO:1)—5914 nucleotides; and size of the human genome—3,000,000,000 nucleotides.

181. To put things into perspective, one dideoxy sequencing reaction can provide the sequence of a DNA fragment that is about 300 nucleotides long. This is only 1/100,000 of one percent of the human genome! Thus, the sequencing reaction has to be initiated precisely at the target DNA sequence.

182. In his declaration, Dr. Jackson compares the process of extracting genes with the process of extracting paper pulp from wood. *See* Jackson, ¶19. *See also* Jackson ¶22. This analogy fails, however, because at least part of the sequence of the gene of interest must be known to allow the researcher or clinician to isolate and sequence the specific gene of interest.

183. To sequence a particular target, at least part of the target sequence must be known to design a suitable primer. The initial sequencing of a target sequence requires ingenuity far beyond the mere application of routine laboratory techniques and usually involves a significant amount of trial and error. A primer is used to initiate the sequencing reaction at the desired location of a target sequence. A primer is an artificial DNA fragment, usually between 15 and 30 nucleotides long, that binds specifically to the target nucleotide sequence. The nucleotide sequence of the primer is complementary to the target sequence such that the bases of the primer and the bases of the target sequence bind to each other. *See* Figure 5 above.

184. Target-sequence specific primers can also be used to initiate polymerase chain reaction ("PCR"), a technique that can be employed to isolate specific target DNA fragments for sequencing. For example, PCR can be used to synthesize a fragment of genomic

DNA. The resulting fragment can then be sequenced. However, to do so, at least part of the sequence of the target DNA molecule must be known so that the target specific primer can be designed. Thus, the use of PCR requires knowledge of at least part of the target DNA sequence to design these specific primers. In the case of *BRCA1* and *BRCA2*, for example, this knowledge has been provided by the inventors of the patents at issue in this case.

185. After diagnostic sequencing, the patient's sample, such as blood or tissue, is no longer blood or tissue but is has been processed to obtain DNA. The DNA has then been subjected to a sequencing reaction. At the end, instead of blood or tissue, the clinician has the chemical structure of a small portion of the patient's DNA.

186. The gene, mRNA and allele are in the body and must be obtained from a patient's tissue sample in order to be sequenced. The cells of the tissue sample must be broken open and a sample of DNA or RNA or allele extracted from the cells. cDNA can be synthesized using mRNA obtained from the patient sample. Various types of patient sample can be used, for example, a blood, tumor tissue, or non-tumor tissue. The DNA has to be isolated from these samples and put through sequencing reactions in order to obtain the sequence. This is transformative—the blood sample no longer resembles blood, and the patient's tissue no longer resembles the tissue.

187. The claimed diagnostic methods transform a deleterious gene buried among the over 25,000 other known genes in the human genome and make it detectable in the clinic. None of the method claims

involve "looking" at genes. One cannot detect or determine a human subject's genes by mere inspection. Detection of a gene marker requires breaking open the cells of a tissue sample, and extracting and excising the native DNA. Using a set of molecular tools, such as a diagnostic probe or a primer that can specifically bind to a BRCA1/2 DNA molecule in a tissue sample, the native DNA is analyzed to determine if the structural composition is the same or different from the normal native gene. These molecular diagnostic tools were designed based on their ability to bind to and form a stable chemical structure with a target gene sequence. Thus, the claimed diagnostic methods are not mere abstract ideas, and cannot be performed by simply looking at a gene.

188. The nucleotide sequence of the human native DNA differs from person to person. Some alterations of the native DNA sequence have no known effects, while others may affect a particular trait, such as eye color. Other alterations may cause disease. Determining a DNA sequence and correlating it with pathological phenotypes can result in such life-saving diagnostics as Myriad's BRAC*Analysis*® test.

189. Alterations of genomic DNA sequences are inherited to the next generation if they occur in the germline. Alterations may also be caused by artificial environmental factors in somatic tissues. Such somatic alterations are normally not passed on to the next generation.

190. Without knowing the correlation between DNA sequence and a disease state, the nucleotide sequence of DNA by itself in a chromosome of a person does not say anything about the disease

susceptibility of that person. Dr. Sulston himself has stated that: "The genome by itself does not provide answers to any of these questions." Sulston, 2002. Rather, extensive statistical analysis is required to identify those alterations in a nucleotide sequence that correlate with a particular medical condition. Nucleotide sequences of a large group of people have to be painstakingly sequenced, analyzed, and correlated with the presence or absence of disease in the carrier of the sequence. This process can take many years.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct.

Executed on: 12/21/2009 /s/ Mark A. Kay

Mark Allan Kay

EXHIBITS 1, 2

[EXHIBITS 1, 2 OMITTED]

[Declaration of Dr. Philip Reilly, filed December 23, 2009] [Caption Omitted In Printing] [Exhibits 1-7 omitted]

I, Philip R. Reilly, hereby declare that:

I. EDUCATION AND BACKGROUND

1. I currently hold the position of Venture Partner at Third Rock Ventures in Boston, Massachusetts. Third Rock Ventures is a venture capital company whose mission is to create transformational life science companies through close collaboration with members of the scientific and business communities. My qualifications, experience, and a list of my publications are set forth in my *curriculum vitae*, attached hereto as Exhibit 1.

2. I am Adjunct Professor of Law at Suffolk University School of Law in Boston, Massachusetts where I teach a seminar in Biomedical Policy and Law. I previously held teaching positions at Cornell University, Tufts University School of Medicine, Harvard Medical School, and Brandeis University. I am a member of the Board of Trustees of Cornell University.

3. I am trained in and have been board certified in both internal medicine and clinical genetics. I have also been a member of the Massachusetts Bar since 1973.

4. I received my J.D. in 1973 from Columbia University in New York, New York and practiced as an attorney from 1975 to 1977 at the law firm of Powers & Hall in Boston, Massachusetts. For a

number of years thereafter, I had a part-time practice at Powers & Hall.

5. I received my M.D. in 1981 from Yale University in New Haven, Connecticut and completed my internship and residency in the Department of Medicine at Boston City Hospital in Boston, Massachusetts. From 1982 to 1983, I was a Professor of Law at the University of Houston. Between 1983 and 1985, I completed my residency. Thereafter, I became a Staff Physician and then, ultimately, Executive Director of the Eunice Kennedy Shriver Center for Mental Retardation, Inc., which was at the time affiliated with Massachusetts General Hospital, in Waltham, Massachusetts.

6. From 2000 to 2006, I was Chairman of the Board and CEO of Interleukin Genetics, Inc. in Waltham, Massachusetts. During the same time, I was also Director of Clinical Genetics. Interleukin Genetics was then and still is a publicly traded company with a focus on developing DNA-based risk assessment tests and preventative and therapeutic products to reduce or ameliorate those risks.

7. I chaired the social issues committee of the American Society of Human Genetics during the 1990's. I also served for three years on the Board of Directors of the American Society of Human Genetics. In my capacity as chair of the social issues committee, I authored or co-authored numerous position papers on important public policy issues related to human genetics that were adopted by the American Society of Human Genetics.

8. I was president of the American Society of Law and Medicine and Ethics (at the time, including

about 3,000 members) in 2002 and 2004. I also served on its Board of Directors.

9. In the 1990's, I was heavily involved in advising leading companies in developing and/or commercializing gene-based diagnostics and therapeutics, including diagnostic tests. This was a time when the field of biotechnology was rapidly developing and a period when many genes were being associated with risk for disease. In particular, many companies turned to me for advice regarding the ethical and legal issues they needed to consider in connection with the new gene based diagnostic tests they were creating. Such companies included, for example, Myriad Genetics, Genzyme Corporation, Collaborative Research, Inc., and Vivigen, Inc. for which I served as a member of the Board of Directors. I further advised biotechnology companies such as Millennium Pharmaceuticals, Inc., GlaxoSmithKline, and Pharmacia.

10. I have served as a member of several advisory boards, including the SmithKline Beecham Genomics Advisory Board, and was Chair of the SmithKline Beecham Clinical Genetics, Ethics and Public Policy Advisory Board. From about 1995 to 2000, I was a member of the Clinical Advisory Board of Myriad Genetics. I assisted Myriad in identifying ethical considerations related to the *BRCA1* and *BRCA2* genetic tests that were developed, and played an important role in developing Myriad's patient consent forms. It was my experience during those years that the entire scientific and clinical team at Myriad showed deep concern for the best interest of patients. For example, Myriad tried to ensure that as many patients as possible had access to the test.

Importantly, Myriad also strived to ensure that patients were given the results of their genetic tests in a responsible and compassionate manner.

11. For several years, I was an advisor to the Biotechnology Industry Organization ("BIO"). BIO is well-regarded and the world's largest biotechnology organization, providing advocacy, business development and communications services for more than 1,200 members worldwide. In my capacity as an advisor, I helped to develop a number of position statements for BIO including in areas such as genetic testing.

12. I am an author of numerous peer-reviewed academic articles and books on topics such as the ethical, legal, and social issues related to genetics. From the 1990's to about 2003, I was frequently a public speaker on the topic of genetics, the future of medicine, and bioethics. I have given approximately 500 speeches on these topics during my career.

13. In my capacity as CEO at Interleukin Genetics, I became familiar with the workings of the United States patent system. I was also involved in drafting or reviewing some of the company's patent applications.

14. I keep apprised of the literature regarding the impact of United States intellectual property law and policy on the development and commercialization of science and technology, particularly with respect to biotechnology.

II. BASIS OF OPINION

15. In preparing this declaration, I have been provided and considered the following: (1) the

Complaint filed in connection with this proceeding; (2) Plaintiffs' Memorandum of Law in Support of Motion for Summary Judgment; (3) Plaintiffs' Rule 56.1 Statement of Material Facts; (4) the Declaration of Dr. Mildred Cho, dated August 17, 2009 ("Cho"); (5) Cho, MK *et al.*, 2003, Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services, *J. Mol. Diagnostics* 5(1):3-8 (cited in paragraph 11 of the Cho Declaration) (Exhibit 2; "Cho 2003"); (6) Merz and Cho, 2005, What are gene patents and why are people worried about them?, *Community. Genet.* 8(4):203-08 (Exhibit 3; "Merz and Cho"); (7) Declaration of Dr. Wendy Chung, dated July 30, 2009 ("Chung"); (8) BIO 2009 Member Survey: Technology Transfer and the Biotechnology Industry, located at http://bio.org/ip/techtransfer/PDF.TECH.TRANSFER.PRESENTATION.10.25.pdf (last printed on December 11, 2009) (Exhibit 4; "BIO Survey"); (9) The Economic Impact of Licensed Commercialized Inventions Originating in Research, 1996-2007: Final Report to the Biotechnology Industry Organization, September 3, 2009, located at http://www.bio.org/ip/techtransfer/BIO_final_report_9_3_09_rev_2.pdf (last printed on December 11, 2009) (Exhibit 5; "BIO Study"); (10) Walsh et al., 2005, "View from the Bench: Patents and Material Transfers" *Science* 309:2002-03 (Exhibit 6; "Walsh"); and (11) Bremer *et al.*, August 14, 2009, The Bayh-Dole Act and Revisionism Redux, Patent, Trademark & Copyright Journal (Exhibit 7; "Bremer").

III. PATENTS PROVIDE THE ESSENTIAL INCENTIVE FOR THE DEVELOPMENT AND COMMERCIALIZATION OF NEW TECHNOLOGIES

16. Patents provide a *bona fide* net social benefit. First, patents are essential in obtaining capital investment in the development and commercialization of technological breakthroughs. Second, patents encourage the sharing of technological advances through the disclosure requirements of the applicable patent laws and regulations, thus enabling the public to take advantage of these developments after the patents expire.

17. The net social benefit provided by patents is especially striking for patents in the life sciences arena. Numerous biotechnology-based clinical applications, especially, gene-based applications, would not be available today without patents. There are many diagnostic tests based on patented isolated DNA molecules or methods of detecting mutations therein. Examples of such tests include the DNA tests for cystic fibrosis (a severe lung disease) which are based on the *CFTR* gene, and for Fragile X syndrome (a leading cause of inherited mental retardation), which is based on the *FMR1* gene. There are today many other DNA based diagnostic tests secured by patents. Similarly, there are many therapeutic products based on patented isolated DNA molecules or their recombinant protein products, including recombinant erythropoietin ("EPO") to treat anemia, and recombinant human granulocyte colony-stimulating factor ("G-CSF") to

treat cancer patients receiving chemotherapy and bone marrow transplants.

18. The patent system is essential to attract investors. Without the incentive provided by the patent system, investors would be much less likely to invest in new and potentially life-saving technologies. Patents, through the promise of a limited period of market exclusivity, provide investors with an opportunity to recoup their initial investment and ultimately, derive commercial benefit therefrom.

19. Indeed, Dr. Mildred Cho has recognized that "[p]atents are clearly seen as a necessary stimulus for the infusion of venture and risk capital in the biotechnology industry . . .." Merz and Cho at p. 6.

20. As Venture Partner of Third Rock Ventures, my work includes the analysis and valuation of intellectual property portfolios and, most importantly, patent portfolios in the life sciences sector. I have come to understand that intellectual property protection is essential to biotechnology and pharmaceutical companies that must invest up to hundreds of millions of dollars in research and development over many years to bring their diagnostic and therapeutic products to market. Patents enable these companies to acquire the capital needed for diagnostic and drug development testing by providing a necessary period of market exclusivity.

21. In the case of genetic testing companies, the limited period of exclusivity provided by a patent is almost always required to secure sufficient capital needed to establish testing capability on a clinical

scale. As CEO of Interleukin Genetics, I personally found this to be the case.

22. I recently reviewed a survey published in 2009 by BIO of 150 biotechnology member companies in the therapeutic and diagnostic healthcare industry. (*See* Exhibit 4, BIO Survey). The survey revealed that the majority of companies (61%) stated they generally in-license projects that are in the pre-clinical or Phase I stage of development, and thus still require substantial R&D investment and commercialization risk by the licensee (*See* Exhibit 4, BIO Survey at 13). A substantial majority (77%) of the respondents without approved products indicated that they expect to spend 5-15 years and over $100 million developing a commercial product (*See* Exhibit 4, BIO Survey at 25, 28). These expenditures far exceed most initial research funding by the federal government.

23. The net social benefit of the patent system accrues both to the biotechnology sector and to the patients it hopes to serve. This is true with regard to patents related to isolated DNA molecules.

IV. PATENTS PROMOTE INFORMATION DISCLOSURE

24. The patenting of human isolated DNA molecules is not in conflict with the notion that science would advance more rapidly if researchers are allowed to take advantage of free access to knowledge. Part of the *quid pro quo* of the patent system is that inventors, in exchange for a limited period of patent exclusivity, must provide a sufficient description of the patented invention so that others may improve upon it.

25. Moreover, patents do not necessarily operate as an absolute monopoly. Although a patent grants the right to exclude others from making, using, and selling or importing into the United States the patented invention for a limited term, the patent holder must still respect the intellectual property rights of third parties in the same field of the invention. Thus, the patentee may not be able to practice the invention covered by the patent without a license from the third party.

26. In addition, the patent system promotes more disclosure than otherwise might occur if, for example, trade secrets were the only means to exclude competitors, at least in the commercial sector. For example, one of the most well-known products sold throughout the world is Coca-Cola (or "Coke"). It is generally known that although various formulas have been introduced since the 1880's, the various formulas have and still are protected by trade secrets. This period of time far exceeds the limited period of market exclusivity that a patents can provide.

V. THE PATENT SYSTEM WORKS AS THE FOUNDING FATHERS INTENDED

27. The Constitution recognizes the need "[t]o promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." United States Constitution, Article 1, Section 8, clause 8.

28. A historical example of the success of the patent system comes from the area of federally funded research. In 1980, in response to concerns

about U.S. competitiveness in the global economy, Congress enacted the Bayh-Dole Act.

29. In 1980, Congress enacted Bayh-Dole to address concerns regarding barriers to commercial development affecting non-governmental entities such as universities and small business firms. Some of the stated objectives of the Act include: (1) utilization of inventions arising from federally supported research or development; (2) to promote collaboration between commercial entities and nonprofit organizations, including universities; and (3) to promote the commercialization and public availability of inventions made in the United States by United States industry and labor. 35 U.S.C. § 200.

30. As reported in the BIO Survey discussed above, the vast majority of the surveyed biotechnology companies license technology from universities (76%) (Exhibit 4, BIO Survey at 17). Moreover, half of the companies surveyed reported that they were founded on the basis of obtaining an in-licensing agreement (Exhibit 4, BIO Survey at 28).

31. Patents also have a significant and positive influence on the United States economy. A 2009 study released by BIO illustrates the importance of university-industry research and development partnerships based on in-licensing of patents. (*See* Exhibit 5; BIO Study). The study reports that university-licensed products commercialized by industry created more than 279,000 new jobs across the United States during the 12-year period between 1996 and 2007 (*See* Exhibit 5, BIO Study at p. 8). Further, the study states that "[w]ithout accounting for product substitution effects, we estimate that

over the period 1996 to 2007, university licensing agreements based on product sales contributed at least $47 billion and [possibly] as much as $187 billion to the U.S. GDP. A moderately conservative estimate based on 5% royalty rates yields a total contribution to GDP for this period of more than $82 billion." (Exhibit 5, BIO Study at p. 32).

32. In a 2009 article published by Bremer and colleagues the authors concluded that "[r]eams of objective data exist supporting the conclusion that the Bayh-Dole Act greatly improved the commercialization of federally-funded research . . . and that the public sector-private sector partnerships which were generated under the [Bayh-Dole] Act are essential both to the well being and the competitive position of the United States." (Exhibit 7, Bremer Article).

33. It is my understanding that the University of Utah Research Foundation, an owner or part-owner of at least some of the patents at issue in this case, obtained federal funding in connection with *BRCA1* and *BRCA2* research. I further understand that Myriad, the exclusive licensee of the patents at issue in this case, developed and commercialized its breakthrough diagnostic tests through the investment of a significant amount of venture and risk capital. The *BRCA1* and *BRCA2* story is just one of the many positive examples of the impact of the Bayh-Dole Act.

34. Further, I believe that the incentives of the patent system were instrumental in Myriad's discovery of the correct *BRCA1* and *BRCA2* sequence and characterization of its true structure, which has

enhanced *BRCA1* and *BRCA2* research by its disclosure to the public.

35. Finally, from my experience in industry, post-invention development costs far exceed pre-invention and research expenditures. In the case of the *BRCA1* and *BRCA2* genes, for example, although the U.S. Government may have granted millions of dollars in the initial research that led to the patents at issue in this case. Myriad almost certainly spent far more in development and commercialization in order to bring its groundbreaking sequencing tests rapidly to the market.

36. Given the immense importance of the existing patent portfolio to the biotechnology industry, it would be far wiser to have any important policy shifts be made prospectively by Congress after sustained public debate. I believe that the policy arguments are better left to the parts of government where they are better addressed—in Congress and in the U.S. Patent and Trademark Office.

VI. PATENTS ON ISOLATED DNA PROMOTE RESEARCH AND ADVANCE CLINICAL DEVELOPMENT

37. Plaintiffs have voiced the concern that gene patents impede scientific research and clinical development by creating an atmosphere of apprehension of patent infringement in the research community. Underlying such concern appears to be the assumption that such patents cover the genes as they are found in the human body.

38. Patents such as the patents-in-suit have served to advance research and the practice of medicine and benefit patients. I am not aware of any

credible evidence that Myriad's patents impede or have impeded basic research.

39. Isolated and purified DNA molecules are chemically, structurally, and functionally different from genes in their native states as they exist in the human body.

40. Thus, the notion that genes and their mutations, alterations, or variations are naturally occurring substances that should not be patented is misplaced. Genes as they are found in the human body are not patentable subject matter.

41. Data cited to support the notion that patents impede research or diagnostic test development is at best inconclusive. This conclusion is echoed in part by an article co-authored by Dr. Mildred Cho. In the article, the authors conclude that "[l]ittle is known about how gene patents are being used and whether they are having a net beneficial or detrimental effect on scientific research and commercial product development." (Exhibit 3, Merz and Cho at p. 6). The authors also state that "[t]here is little evidence that early fears about gene patenting placing substantial restraints on research and clinical medicine have come to fruition." (Exhibit 3, Merz and Cho at Abstract, p. 1).

42. Further, in a 2005 article published in the journal *Science*, John P. Walsh and colleagues report the findings from a survey conducted on 414 biomedical researchers in universities, government, and nonprofit institutions to determine the effect of patents on biomedical research and material transfers. (Exhibit 6, Walsh at p. 2002). The researchers found that "few academic bench

scientists currently pay much attention to the others' patents." *Id.* Moreover, of the "32 respondents who were aware of relevant IP, four reported changing their research approach and five delayed completion of an experiment by more than one month. No one reported abandoning a line of research. Thus, of 381 academic scientists . . . none were stopped by the existence of patents, and even modifications or delays were rare." *Id.*

43. The sheer volume of scientific publications on BRCA1/2 genes and their gene products belies the purported impediment in basic research. On December 10, 2009, I performed a search using the term "BRCA1" in the PubMed database[81] which retrieved almost 7,000 references. A similar PubMed search conducted using the term "BRCA2" retrieved over 4,000 references.

44. Moreover, the *BRCA1* and *BRCA2* patents at issue in this case do not appear to have impeded clinical research. A search on the website ClinicalTrials.gov[82] on December 19, 2009 using the term "BRCA1" retrieved 77 clinical trials that have been completed, are ongoing, or are actively recruiting subjects. Using the search term "BRCA2,"

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[81] PubMed at the website pubmed.org is a free search engine for accessing citations, abstracts and some full text articles on life sciences and biomedical topics. PubMed is maintained by United States National Library of Medicine at the National Institutes of Health.

[82] ClinicalTrials.gov is a registry of federally and privately supported clinical trials conducted in the United States and around the world. It is a service provided by the National Institutes of Health.

58 clinical trials were retrieved that have been completed, are ongoing, or are actively recruiting subjects.

45. From my experience, the sharing of research tools was not inhibited by IP protection. For example, during my tenure as Executive Director at the Eunice Kennedy Shriver Center for Mental Retardation, an institute that focused on neuroscience research, the scientists with whom I had the privilege to work routinely acquired valuable substances, materials, and information under material transfer agreements from both academe and industry.

46. I note that in her declaration, Dr. Cho concludes that "patents on genes used for clinical diagnostics inhibit the conduct of research to further the development of improvements to genetic tests." Cho ¶ 24. I strongly disagree. I would be curious to see how Dr. Cho herself would reconcile her statement quoted above with her own article published just a few years ago, which states that "[t]here is little evidence that early fears about gene patenting placing substantial restraints on research and clinical medicine have come to fruition." (Exhibit 3, Merz and Cho at p. 6).

47. Moreover, I note that the surveys conducted by Dr. Cho and cited in her declaration included many clinical geneticists who were involved in or overseeing genetic testing laboratories that were intended to generate a profit. Thus, many of these geneticists charge for genetic testing themselves. For example, in her 2003 article, Dr. Cho and colleagues performed a telephonic survey of all laboratory directors in the United States who were

members of the Association for Molecular Pathology ("AMP") or who were listed on the GeneTest.org website. (Exhibit 2, Cho 2003 at p. 3). I further note that AMP is a plaintiff in the present proceeding. I believe that the study was biased towards individuals or laboratories many of whom stand to gain should the patents at issue become invalidated.

48. The results obtained through Dr. Cho's telephonic survey published in 2003 at most represent a snapshot of opinions of a 122 laboratory directors at that time. (Exhibit 2, Cho 2003 at p. 3). Dr. Cho was clearly aware of the limitations of her own study. She concluded that "our data do not directly address the question or whether patents and restrictive licensing practices have affected the cost and quality of genetic tests, or hindered new research." (Exhibit 2, Cho 2003 at p. 8).

49. Based on the above, any concerns that human "gene" patents impede basic scientific and/or clinical research are not supported by the evidence. The sheer amount of research being conducted and the number of scientific articles being published regularly on the *BRCA1* and *BRCA2* genes and their protein products, for example, provide strong evidence that research is not impeded.

VII. PATENTS ON ISOLATED DNA PROMOTE ADVANCES IN MEDICINE AND ENHANCE THE QUALITY OF PATIENT CARE

50. Another concern voiced by Plaintiffs is that "gene" patents impede advancements in medicine and clinical development. Again, Dr. Cho was clearly aware of the limitations of her own study. She

concluded that "our data do not directly address the question or whether patents and restrictive licensing practices have affected the cost and quality of genetic tests, or hindered new research." (Exhibit 2, Cho 2003 at p. 8).

51. The reality is quite the opposite. As discussed above, without the promise of a period of market exclusivity provided by patents and the infusion of venture and risk capital derived therefrom, companies that capitalize on innovation simply would not be created. Their products would not be brought to market, to the clinic, and most importantly, to patients. This of course, holds true for companies such as Myriad and its *BRCA1/2* diagnostic tests.

52. Intellectual property is essential to innovation in health care. In my capacity as venture partner, I help to start companies that develop treatments for rare genetic disorders for which there is no adequate current therapy. An example is a company to develop a recombinant protein to treat a rare genetic disorder, namely X-linked hypohidrotic ectodermal dysplasia. The decision to fund this company with significant capital was critically dependent on an assessment of the quality of the relevant intellectual property. Without the promise of a period of market exclusivity provided by the patent law, this investment would not have been made.

53. Without strong patent protection, the many biotechnology-based medical advances, such as Myriad's *BRCA1/BRCA2* genetic based testing, would not be developed.

54. Yet another concern voice by the Plaintiffs about "gene" patents is that they harm patients by interfering with their ability to get a second opinion and to make informed decisions about their health and medical care. I disagree. Indeed the term "second opinion" is not used properly. In the clinic, the term "second opinion" is used to refer to the interpretation of diagnostic tests and their implications for treatment. It would be quite unusual to have a patient's DNA sequenced a second time in a second laboratory. If, however, there were any doubts regarding the accuracy of the test, re-sequencing with the proper controls would normally be performed by the original provider. The term, second opinion, generally refers to the interpretation of a test result and which therapeutic options to follow based thereon.

55. As an internist and clinical geneticist, it is my understanding that once a patient has his or her genes sequenced, *e.g.*, the *BRCA1* and/or *BRCA2* genes, the patient generally does not get his or her genes re-sequenced. In the absence of any doubts regarding the accuracy of the original test, re-sequencing of the patient's genes would be an unnecessary use of resources.

56. The situation is analogous to a person who obtains an MRI and whose physician then diagnoses a disorder and subsequently recommends a course of treatment. The patient is free to take the MRI images to another physician for a second opinion. Again however, obtaining another MRI just a short time thereafter would be an unnecessary use of resources, and it is unlikely that an insurance plan would cover a second MRI.

VIII. TEST RESULTS GENERATED IN RESEARCH LABORATORIES SHOULD NOT BE COMMUNICATED TO PATIENTS

57. Plaintiffs have complained that because of the patents at issue in this case, they are unable to share the results of any genetic testing performed and that this goes against their ethical obligations. In particular, Dr. Chung in her declaration states the following: "[a]s a researcher, I believe I have an ethical responsibility to offer my test subjects access to information about their genes. In order to meet this ethical responsibility, I offer my research subjects the option of finding out their results. As a result of the patents, I can only do that by sending samples to Myriad Genetics to test the sample [*sic*] so I can communicate that information to the patients." Chung ¶14.

58. While I respect Dr. Chung's eagerness to help her "test subjects," Dr. Chung appears to confuse information generated during the course of research with information generated within a legally certified diagnostic laboratory. I believe it would be illegal to provide results of genetic testing for clinical use if the laboratory is not Clinical Laboratory Improvement Amendments ("CLIA")-certified. In order for a laboratory to provide a clinical test result to a patient, it must be CLIA-certified. In addition, New York State, where Dr. Chung operates her research laboratory, imposes additional licensing requirements on DNA testing, which could take, in my personal experience, a year or more to satisfy.

59. It is my impression, based on many years of interacting with academic researchers, that the

majority of academic researchers operating laboratories (as opposed to CLIA-certified laboratories) do not believe that they should share test results with subjects outside of the standard clinical setting.

IX. PATENTS SUCH AS THE ONES AT ISSUE ARE CRITICAL TO A NASCENT AND BURGEONING INDUSTRY

60. I believe that the emerging field of personalized medicine promises dramatic improvements in health care. The opportunity to develop new therapies based on the genetic dissection of complex disorders raises the realistic hope for individualized treatment plans.

61. The future of personalized medicine will require understanding the biological and physiological significance of variations in genes like *BRCA1* and *BRCA2*, and designing ways to use them in preventative and therapeutic interventions. By identifying and targeting faulty genes before they wreak havoc in the cells of the human body, medicine has the chance to save countless lives.

62. Patents upon the Myriad inventions, and similar ones, have had and will continue to have a positive impact on clinical practice and research. The granting of patents in this area has not had a negative impact on breast or ovarian cancer research and clinical practice, and clinical practice has not been harmed. To the contrary, patents on these isolated molecular diagnostic tools are important, indeed essential, to create the incentives for the immense effort involved in their discovery, and for the expense involved in bringing them to market.

The incentives provided by patents fuel discovery and commercialization in emerging technologies such as medical diagnostics, resulting in social and health benefits for future generations.

The views expressed herein are my own and should not be construed in any way to represent the views of Third Rock Ventures.

Pursuant to 28 USC § 1746, I declare under penalty of perjury that the foregoing is true and correct.

/s/ Philip R. Reilly
Philip R. Reilly

Executed on December 21, 2009

EXHIBITS 1-7

[EXHIBITS 1-7 OMITTED]

[Declaration of Joseph Schlessinger, filed December 23, 2009] [Caption Omitted In Printing] [Exhibits 1, 2 Omitted]

I, Joseph Schlessinger hereby declare that:

1. I am the Chairman of the Department of Pharmacology at Yale University School of Medicine and William H. Prusoff Professor since 2001. Prior to my appointment at Yale, I was the Director of the Skirball Institute for Biomolecular Medicine at New York University (NYU) Medical Center from 1998–2001 and the Milton and Helen Kimmelman Professor and Chairman of the Department of Pharmacology at NYU Medical School from 1990–2001. I was also a member of the faculty of the Weizmann Institute from 1978–1991 and the Ruth and Leonard Simon Professor of Cancer Research in the Department of Immunology from 1985–1991. My qualifications, experience and list of my publications are set forth in my curriculum vitae attached hereto as Exhibit 1. (Ex. 1)

2. I received a B.Sc. degree in Chemistry and Physics in 1968 (magna cum laude), and a M.Sc. degree in chemistry (magna cum laude) in 1970 from the Hebrew University in Jerusalem. I obtained my Ph.D. degree in biophysics from the Weizmann Institute of Science in 1974. From 1974–1976, I was a postdoctoral fellow in the Departments of Chemistry and Applied Physics at Cornell University, and from 1977–1978, I was a visiting fellow in the immunology branch of the National Cancer Institute of NIH.

3. In addition to my academic appointments, I was a Research Director at Meloy laboratory in

Rockville, Maryland and later on in Rorer Biotechnology in King of Prussia, Pennsylvania from 1985–1990. Thereafter, I co-founded Sugen, Inc. in 1991. One of the pipeline products developed at Sugen (SU11248) was ultimately approved by the FDA (Sutent or Sunitinib) for treating gastrointestinal stromal tumors, renal cell carcinoma and endocrine pancreatic cancer . In 2001, I co-founded Plexxikon, a company that uses a pioneering structural biology-based platform for drug discovery. I am currently the Chairman of the Board and a member of the Scientific Advisory Board of Plexxikon. In 2008 I founded Kolltan, a company that uses a novel approach for developing a new generation of therapeutic antibodies that block the activity of oncogenic receptor tyrosine kinases

4. I received the following awards: Michael Landau Prize (1973), Sara Leady Prize (1980), Hestrin Prize (1983), Levinson Prize (1984), Ciba-Drew Award (1995), Antoine Lacassagne Prize (1995), The Distinguished Service Award of Miami Biotechnology in (1999), Honorary Membership of the Japanese Biochemical Society (1999), Taylor Prize (2000), Honorary Doctor of Philosophy from the University of Haifa (2002) and the Dan David Prize (2006).

5. I was elected to the National Academy of Sciences in 2000, to the American Academy of Arts and Sciences in 2001, and as Member of the Institute of Medicine of the National Academies in 2005. I am a member of the European Molecular Biology Organization (EMBO) (1982), a fellow of the Neuroscience Research Program (2000) and a member of the European Academy of Sciences (2004).

6. I serve on the editorial boards of numerous journals, including Cell, Molecular Cell.. the Journal of Cell Biology, and the Science magazine 'Science Signaling' journal. I have authored over 450 scientific original and review articles in the area of molecular biology, biochemistry, structural biology and drug discovery, mostly in the area of tyrosine kinase signaling.

7. I have delivered many named lectures including The Fourth Kroc Lecture, Harvard Medical School (1988); E.J. Cohn Lecture, Harvard Medical School (1993); E. Fisher Lecture, University of Geneva (1993); Lamport Lecture, University of Seattle (1993); Harvey Lecture, Rockefeller University (1994); Deans Lecture, Mount Sinai Medical School (1994); Feigen Lecture, Stanford University (1994); Randall Lecture, University of Pennsylvania (1994); Sigma Tau Lecture, Rome, Italy (1995); Lindner Lecture, Weizmann Institute (1996); Burroughs Wellcome Lectures, University of Indiana (1997); Juan March Lecture, Madrid, Spain (1998); Bayer Lecture, Berkeley (1999); Sixth Kroc Lecture, University of Massachusetts (1999); NIH Director Lecture (2000); K.F. Naidorf Lecture, Columbia University (2000); Distinguished Speaker, University of Texas, San Antonio (2000); Severo Ochoa Lecture, Madrid, Spain (2000); First Alton Meister Lecture, Cornell University (2001); Fritz Lipmann Lecture, German Society for Biochemistry and Molecular Biology (2001); Karl Beyer Lectures, University of Wisconsin, Madison (2003); Asher Rothstein Lecture, The Hospital for Sick Children Research Institute, Toronto, Canada (2003); and the Distinguished Lecture on Molecular Targets for

Cancer Prevention. AACR, Baltimore, Maryland (2005).

8. My area of research has focused on signaling through tyrosine phosphorylation, which is important in many areas of cellular regulation, especially growth control and cancer. My studies have led to an understanding of the mechanism of transmembrane signaling by receptor tyrosine kinases and how the resulting signals are transmitted within the cell to regulate gene expression, control cell growth and differentiation. Tyrosine kinase signaling plays a critical role in the control of many cellular processes including gene expression, cell proliferation, differentiation, metabolism, as well as cell survival and migration. Tyrosine kinases play a particularly important role in cancer, and several agents that block their activity are now used as anti-cancer drugs, such as Gleevec, Sutent and many others.

9. I reviewed the following documents: Plaintiffs' Memorandum of Law in Support of Motion for Summary Judgment ("Memo"); Plaintiffs' Rule 56.1 Statement of Material Facts ("SMF"); Declaration of Sir John Sulston, Ph.D. of August 17, 2009 ("Sulston"); Declaration of Christopher E. Mason of August 20, 2009 ("Mason"); and Declaration of Myles W. Jackson of August 18, 2009 ("Jackson").

10. As a scientist practicing in both the academic and industrial biotechnology/pharmaceutical arenas, I have experience with patents. I am a named inventor on a number of patents relating to screening methods and therapeutics. I have been asked to share my observations on the impact that patents have on research and development in the

biotechnology field, and the role that patents have in bringing diagnostic and therapeutic products to the market making them available to patients. I am not a lawyer and express no legal opinion.

BACKGROUND

11. By way of background, genes are hereditary units contained within chromosomes – threadlike parts of the nucleus of cells in the body. The body does not have a mechanism for isolating genes, contrary to what I read in the Memo at p. 25 citing Jackson, ¶¶ 26-31 and Mason ¶¶ 11-12. A gene is part of a chromosome and is always surrounded by proteins.

12. Chromosomes are composed of DNA (deoxyribonucleic acid) and proteins. DNA is a chemical composition -- a polymer of building blocks called "nucleotides". Each nucleotide is composed of a deoxyribose sugar, a phosphate and one of four nitrogenous bases: adenine (A), guanine (G), thymine (T), and cytosine (C). DNA is double stranded and the strands are crosslinked via the bases – A always links with T and G always links with C. A DNA molecule can be characterized by the sequence of the bases in the DNA polymer.

13. A gene on its own cannot do anything – other parts of the cell are required for a gene to have its biological effect. In general, this is to make one or more proteins vital to the structure and function of cells in the body. To do this, the gene's DNA is first copied or "transcribed" into RNA (ribonucleic acid) – a polymer of nucleotides that differ from DNA, each unit composed of a ribose sugar, a phosphate and one of four bases: adenine (A), guanine (G), uracil (U),

and cytosine (C). For transcription, the DNA "unzips" and one of the DNA strands serves as the template for RNA assembly – A always links to U; G always links to C. The RNA transcript is then processed to form messenger RNA (mRNA) that is "translated" into a polypeptide (another biopolymer composed of building blocks called amino acids) which is a component of proteins responsible for the functions vital to the cell.

14. The RNA transcribed from a gene is processed into one or more messenger RNAs ("mRNAs") through a process called splicing in which portions of the RNA transcript that are not required for protein production are removed. Alternative splicing is a process in which different portions of the RNA transcript are reconnected in multiple ways. These different mRNAs resulting from transcription of one gene may then be translated into different polypeptides. Thus, a single gene may code for multiple mRNAs and protein products.

15. Using enzymatic reactions, a DNA molecule can be synthesized that is complementary to an mRNA (cDNA). But this DNA molecule would capture only one splice variant expressed from the gene. Thus, contrary to statements made by the plaintiffs, a cDNA is not necessarily informationally identical to the gene in the body. The plaintiffs' basis for this -- the old dogma of "one gene, one enzyme" -- is dead. SMF, ¶¶ 59, 61, 62; Mason, ¶¶ 9, 28-29, 32-33.

DECIPHERING THE STRUCTURE OF A GENE AND FUNCTION OF ITS PRODUCTS

16. Deciphering the structure of a gene and the function of its products is very relevant for diagnostics and drug development. If you do not know the sequence of a gene and the function of its products, you cannot design diagnostics and therapies to treat patients. The genome has been sequenced and published. But the raw sequence data does not tell you where a particular gene is exactly located and most importantly, the structure and function of the protein or proteins expressed from the gene.

17. I am puzzled by Dr. Sulston's view that an isolated DNA molecule cannot be an invention. He seems to rationalize his conclusion by simplifying DNA to an arrangement of letters that carries biological information dictated by nature that is identical to the information of its genomic counterpart. *See* Sulston, ¶¶ 10-19. Categorizing isolated genes as natural products/information that should be relegated to the public domain seems to me a bit superficial.

18. If you look hard enough, all things have natural origins. There are many examples of "natural products" that have been patented. Some examples of patented, small molecule "natural products" are antibiotics (*e.g.*, penicillin), chemotherapeutics (*e.g.*, taxol, mitomycin C) and statins (*e.g.*, lovastatin). Larger biomolecular "natural products," *i.e.*, proteins, have been patented as well, such as antibodies, erythropoietin, interferon and proteins that control blood clotting such as tissue plasminogen activator (TPA), streptokinase, and

urokinase. DNA molecules whose biological function has been revealed by research should be treated in the same manner. There is no difference between discovering the function of a gene and developing a diagnostic, and discovering a new natural chemical product and developing a new drug.

19. I disagree with Dr. Sulston's assessment that DNA is only information. *See* Sulston, ¶ 13-17. DNA is not merely a linear digital code consisting of a sequence of letters. DNA is a chemical composition – a polymer of building blocks called nucleotides. Each nucleotide is composed of a deoxyribose sugar, a phosphate and one of four nitrogenous bases: adenine, guanine, thymine and cytosine. Those bases are represented by the letters A, G, T, and C, respectively. The letters are just designations assigned to the nucleotides so that we can easily depict a DNA molecule. This system is analogous to the chemical formulas we use for describing other chemical compounds. For example, the chemical formula for water is H_2O, where "H" represents a hydrogen atom, "2" represents the number of hydrogen atoms present in the compound, and "O" represents an oxygen atom.

20. Sequencing the genome yields information that is fantastically important, *but* it does not tell you the exact location of the gene and most importantly what function is specified by the gene or by a mutated disease causing gene. I can understand why one should not be allowed to patent DNA without having any knowledge about its function, but an isolated DNA where the function of its products has been determined is a different story here, an invention has been made. Moreover, if you figure out

a direct link or an association between a gene sequence and a cause for or if you figure out the correlations or associations between a gene sequence and an increased risk for a specific disease, this discovery can be used to develop diagnostics and drugs that help people. I do not see any reason why a patent should not be awarded for such inventions.

21. To decipher the function of the proteins expressed from a gene takes a lot of work, ingenuity and luck. We have only 20,000 genes (humans have fewer genes than rice!). To manage all of the traits manifested by a human being, strategies evolved to use the limited supply of genes to provide all the functions needed by the body. For example, alternative splicing of RNA transcribed from a gene is a mechanism the cell uses to generate multiple mRNAs and their encoded protein products from each gene to provide the functions necessary for survival. Alternative splicing greatly increases the diversity of proteins that can be encoded by the genome.

22. In my field, there are approximately 518 genes that encode for protein kinases. On average, five alternatively spliced products result from the expression of each protein kinase gene, and this does not take into account the post-translational modifications of the resulting polypeptides and proteins which lead to regulation. Thus, there are at least 2,500 forms of protein product(s) that result from the expression of over 518 genes that encode the protein kinases.

23. In other situations, fully functional proteins are encoded by two or more genes. For example, antibodies, receptors, ion channels and many other

proteins are composed of multiple polypeptides each encoded by different genes, *e.g.*, mammalian cytochrome c oxidase has 13 different polypeptide subunits with 3 being coded by a mitochondrial and nuclear genes and 10 by a nuclear gene. Tomitake Tsukihara, *et al.*, 1995, "Structures of Metal Sites of Oxidized Bovine Heart Cytochrome *c* Oxidase at 2.8 Å" *Science* 269:1069-1074 (Exhibit 2).

24. One approach to deciphering the function of a protein is to isolate or synthesize the DNA containing the gene and use it to produce protein product(s) to study their biochemical functions. This requires first deciphering the sequence of the gene responsible for expression of the protein.

25. In another approach, you can use genetics to eliminate the gene from the genome of a cell or laboratory animal (sometimes referred to as "knocking out" the gene). If you are lucky and the gene is not redundant, you can figure out what the gene product does by observing the loss or gain of biochemical or physiological function in the cell or animal. For example, for tumor suppressor genes, like the BRCA genes, the elimination of the gene in these experiments should result in a loss of the protective function and increase the animal's risk for developing cancer.

26. In my view, a scientist who, using his ingenuity and aided by a little luck, spends a great deal of time and effort to investigate and discover what a gene product does and how to use it, has made an invention.

27. Once the scientist has deciphered the function of the gene's products, synthetic DNAs can be

designed for diagnostics, cells can be engineered for drug screening, and therapeutics can be developed. The isolated DNA acquires functions it did not have as a gene in the body. Unlike genes in the body which are chemically bound in the chromosomes, isolated DNA molecules or their fragments can be used as a probe or primer for diagnostics, to synthesize proteins for therapeutic use, and/or for drug screening.

28. A probe or a primer can be used to detect target DNAs or RNAs based on its ability to bind, *i.e.*, hybridize, to its complementary nucleotide strand. A nucleotide strand is complementary to another when the bases of one strand are properly paired with the bases of the other, *i.e.*, A always pairs with T (U in RNA) and G always pairs with C. For example, the complementary strand to a DNA molecule represented by ATCG will be depicted as TAGC.

29. An isolated DNA molecule can be used as a probe to identify target DNAs or RNAs in sample that are complementary to the arrangement of the probe's bases. In this application, the DNA probe is tagged with a molecular marker, *e.g.*, a radioactive isotope, and contacted with the sample under appropriate conditions to allow for hybridization. After washing away unbound material, the detection of the radioactive isotope in the sample indicates hybridization of the DNA probe to a complementary target.

30. An isolated DNA can also be used as a primer to amplify a specific region of a DNA strand (the DNA target) by a process called polymerase chain reaction ("PCR"). In this approach, primers

complementary to the target region along with an enzyme called DNA polymerase are added to a sample under appropriate reaction conditions. The primer serves as a starting point for synthesis of a new DNA strand complementary to the target DNA which serves as a template. The reaction is repeated to allow for amplification of the synthesized fragments. A gene in the body cannot be used as a probe or primer.

PATENTS ARE CRITICAL FOR RESEARCH AND DEVELOPMENT

31. In my experience in the biotechnology industry, companies would not be able to raise money to do the research needed to develop diagnostic and therapeutic products without patent protection. Scientists involved in the Human Genome Project have been very fortunate to have the financial backing of organizations such as the Wellcome Trust. Ironically, the income used to establish the Wellcome Trust was derived from Burroughs Wellcome, a pharmaceutical company that amassed a fortune selling patented drugs. Most institutions do not have the luxury of a trust fund, and need patent protection to obtain investments and funding. If these institutions cannot raise the capital to start companies or invest in research and development, promising new diagnostics and therapeutics will not be developed.

32. Moreover, without patent protection, large pharmaceutical and diagnostic companies would not take a drug or diagnostic test through clinical trials and to market. As a result, discoveries that would otherwise help patients, would remain a mere

laboratory curiosity. The exclusivity that patents afford is the incentive for the large pharmaceutical companies to take the risk of investing large quantities of money to take a candidate drug or diagnostic through expensive clinical trials.

33. Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct.

/s/Joseph Schlessinger

Joseph Schlessinger, Ph.D.

Executed on December 21, 2009

EXHIBITS 1, 2

[EXHIBITS 1, 2 OMITTED]

[Declaration of Dr. Donna Shattuck, filed December 23, 2009] [Caption Omitted In Printing] [Exhibits 1, 2, 4-6 omitted]

I, Donna Shattuck, declare under penalty of perjury:

1. I received my B.A. in Biology from SUNY Binghamton, my Ph.D. in Microbiology in 1982 from the University of Virginia, and performed postdoctoral training at Washington University in St. Louis. A copy of my curriculum vitae and a list of my research publications are attached as Exhibits 1 & 2, respectively.

2. I was employed by Myriad Genetics, Inc. between July 1, 1993 and July 1, 2009. At Myriad I held several senior positions, including Vice President of Population Genetics at the time of my departure.

3. I was personally involved in the identification of the *BRCA1* gene as a breast and ovarian cancer susceptibility gene. In that project, I led the mutation screening effort, resequencing the newly isolated **candidate genes to detect mutations that co-segregate with breast cancer cases. I am one of the named** inventors in United States Patent Nos. 5,693,473, 5,709,999, 5,710,001, 5,747,282, & 5,753,441.

4. The identification of *BRCA1* required the positional cloning approach. In positional cloning of the *BRCA1* gene, the following steps were necessary:

   (a) obtaining DNA samples from large, well-documented families with inherited breast cancer;

(b) discovering appropriate polymorphic markers in the *BRCA1* region;

(c) typing individuals from suitable families with suitable polymorphic markers to yield a sufficiently small chromosomal region containing the *BRCA1* gene;

(d) identifying gene structures within that small chromosomal region; and

(e) identifying causal mutations in the gene structures that segregate with breast cancer in a statistically significant manner, but not with control or non-cancer patients.

5. Each of the above steps required substantial effort and technical difficulties had to be overcome in each. Indeed, the *BRCA1* gene would not have been identified had failure occurred in any one of the identified steps.

THE ART TAUGHT SEVERAL DIFFERENT GENOMIC REGIONS FOR *BRCA1*

6. Even in September of 1994, when Myriad and its collaborators (the University of Utah and the NIEHS, an institute within the NIH) had identified the *BRCA1* gene, there was still a great deal of puzzling information in the public domain with regard to the chromosomal location of the *BRCA1* gene. Such puzzling information led to a general state of confusion and frustration within the field.

7. For example, as shown in Exhibit 3, while Albertsen et al.[1] disclosed that BRCA1 was located between markers D17S776 and D17S78, Smith et al.[2] taught that *BRCA1* should be between D17S702 and EDH17D, which region does not actually contain the *BRCA1* gene. Moreover, Jones et al.[3] suggested that the *BRCA1* gene was in the region between 1A1.3B and D17S78, which is actually distal to the *BRCA1* gene. In addition, Cropp et al.[4] incorrectly localized *BRCA1* to a small region between D17S846 and D17S746.

8. Given the confusion, a skilled artisan would not have known in which chromosomal region to look for the *BRCA1* gene. Indeed, it would have required a great deal of effort to analyze and identify genes in each of the suggested regions and to then determine if the genes harbor mutations that co-segregate with breast cancer in individual members of breast cancer families (kindreds).

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[1] Albertsen *et al.*, *A physical map and candidate genes in the* BRCA1 *region on chromosome 17q12-21*, NAT. GENET., 8:387-91 (1994).

[2] Smith *et al.*, *Localisation of the breast-ovarian cancer susceptibility gene* (BRCA1) *on 17q12-21 to an interval of < or = 1 cM*, GENES CHROM. CANCER, 10:71-6 (1994).

[3] Jones *et al.*, *The detailed characterisation of a 400 kb cosmid walk in the* BRCA1 *region: identification and localisation of 10 genes including a dual-specificity phosphatase*, HUM. MOL. GENET., 11:1927-34 (1994).

[4] Cropp *et al.*, *Evidence for involvement of BRCA1 in sporadic breast carcinomas*, CANCER RES., 54:2548-51 (1994).

EXTENSIVE FAMILY PEDIGREE ANALYSIS AND SAMPLE COLLECTION WERE CRITICAL THROUGHOUT THE SEARCH FOR *BRCA1*

9. One of the keys to the Myriad Collaboration's success in characterizing *BRCA1* was the large, well documented, and highly informative collection of family pedigrees (breast and ovarian cancer kindreds) it had in its possession, and the numerous DNA samples obtained from many members of these kindreds. This was particularly important because during the period of the discovery of *BRCA1*, competition and rivalries between research groups led to the competing groups fervently protecting their samples and kindreds, and not sharing kindreds and samples with each other.

10. Large and informative kindreds are essential for successful linkage analysis. The families need be large in order to provide sufficient statistical power for the analysis. The families need be informative, i.e., exhibiting clear co-inheritance of mutations within the *BRCA1* gene with the disease, such that segregation of a *BRCA1* susceptibility allele can be deciphered by statistical means. As a matter of fact, even some large families with a large number of individuals afflicted with breast cancer were more confusing than helpful in the search for *BRCA1*. This is because the cancer running through these families could have been due to susceptibility genes other than *BRCA1*. For example, Exhibit 4 illustrates that Kindreds 1911 and 1927 both have over 9 affected individuals, yet the LOD scores derived from these families were not useful in identifying *BRCA1* by linkage analysis.

11. It was well-recognized in the field that the Myriad Collaboration had gathered and characterized the largest and best breast cancer kindred collections. This was largely due to decades of extensive effort by Dr. Mark Skolnick, a pioneer of family collection and pedigree analysis for linkage analysis. *See* D. Skolnick. Dr. Skolnick was the leader of the Myriad Collaboration and is a named inventor in United States Patent Nos. 5,710,001, 5,747,282, & 5,753,441.

12. Indeed, our Kindred 2082 was the largest and best breast cancer kindred known. As shown in Exhibits 4 and 5, Kindred 2082 has 51 breast cancer cases and 22 ovarian cases. With kindreds such as Kindred 2082, as well as other inventive approaches, we were able to narrow the putative *BRCA1* region to about 600 kb by linkage analysis, thereby making the isolation and of the *BRCA1* gene possible.

13. The large and informative family collections in the Myriad Collaboration's possession were also critical in identifying mutations in the *BRCA1* gene that co-segregated with disease in the breast and ovarian cancer pedigrees.

14. Again as illustrated by Kindreds 1925, 1911 and 1927 in Exhibit 4, some families don't harbor *BRCA1* mutations, even though they have a large number of apparently inherited breast cancer cases. If a skilled person only had such families in their collection, and even if he or she were able to isolate a small portion of the chromosome harboring a breast or ovarian cancer risk gene through linkage analysis and candidate gene isolation, he or she would still have not been able to recognize that that gene is indeed the *BRCA1* gene. Unlike the process of

isolating genes based on biochemical functions (e.g., erythropoietin gene), a disease gene is identified via positional cloning only when a causal mutation that exists within that gene is found to co-segregate with the disease in question.

SUITABLE FAMILIES WITH USEFUL POLYMORPHIC MARKERS HELPED NARROW DOWN A WORKABLE CHROMOSOMAL REGION CONTAINING THE *BRCA1* GENE

15. In this respect, it is worth noting that after we isolated a candidate gene which corresponded to the *BRCA1* gene, we selected 8 priority families for mutation screening or resequencing. 5 of these families were found to harbor segregating *BRCA1* mutations. In three of these families, the mutations were either a nonsense change (i.e., a stop codon) or frameshift mutations resulting in premature stop codons. Such mutations immediately informed us that they are deleterious mutations that result in alterations in the structure and functions of the protein encoded by the gene, which is consistent with a tumor suppressor mutation resulting in the phenotype of breast cancer. In fact, at the time this work was being conducted *BRCA1* was suspected to be a classic tumor suppressor gene like the p53 gene.

16. With the technology available in 1994, only a limited number of families could be comprehensively screened for mutations. Having large and informative families and correctly choosing the families for resequencing were extremely important technical decisions that lead to the Myriad Collaboration's success.

THE MYRIAD COLLABORATION DEFIED CONVENTION IN ITS SEARCH FOR *BRCA1*

17. Another step we undertook that, in hindsight, appeared to be critical to our success was that in addition to yeast artificial chromosomes (YACs), we used P1 and BAC clones in candidate gene identification. This was in contrast to both the general custom in the art of using only YACs in positional cloning,[5] and to our competitors' touting the use of YACs and cosmids specifically in the *BRCA1* effort.[6]

18. YACs were commonly used in the art because they can accommodate large genomic DNA fragments (100-1000 kb), thereby making genomic cloning and gene identification and analysis within a large chromosomal region more convenient due to their sheer size. It was also thought that the size of YACs would make it more likely that an entire gene would be contained within one or very few YAC clones.

19. BACs (bacteria artificial chromosomes) are bacteria-based and can accommodate, on average, inserts of about 150kb, while bacteriophage-based P1 clones typically have inserts of about 50-85 kb.

20. We used P1 and BAC clones to physically map the *BRCA1* region, to partially sequence the genomic

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[5] Watson, James D., Gilman, M., Witkowski, J.A., and Zoller, M. 1992. *Recombinant DNA*, 2nd edition. pp. 590-4. Scientific American Books, New York.

[6] *See* Weber *et al.*, *Familial breast cancer. Approaching the isolation of a susceptibility gene*, CANCER, 74:1013-20 (1994); Friedman *et al.*, *The search for* BRCA1, CANCER RES., 54:6374-82 (1994); Jones *et al.*, *supra* note 3.

DNA, and to isolate cDNAs, primarily because we recognized that they were more stable and more manageable in size. Indeed, at least three of the nine YACs isolated in our *BRCA1* physical mapping studies contained deletions.[7] More illustrative is the fact that the group led by Mary-Claire King recognized after our publication of the *BRCA1* gene that the YAC-derived genomic clone they were analyzing actually had a deletion at the site of the BRCA1 gene. Indeed, Dr. Mary-Claire King proclaimed in one scientific conference after our discovery of the *BRCA1* gene that "P1 and BACs are the winners of the day."

21. It was later recognized that the genomic DNA in the *BRCA1* region has one of the highest densities of Alu repeats ever reported. Smith et al.[8] examined 326 loci in GenBank for repeat structures. Only three genes have Alu densities greater than *BRCA1*.[9] Alu repeats are well known to cause large DNA rearrangements such as deletions and duplications. Apparently, the high density of Alu repeats in the *BRCA1* region exacerbated the problem of instability and insert rearrangements associated with YACs, but all of this is based on hindsight (i.e., the Alu repeats were only discovered because we provided the structure of the gene). At the time we selected

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[7] *See* Harshman *et al.*, *Comparison of the positional cloning methods used to isolate the BRCA1 gene*, HUM. MOL. GENET., 4:1259-66 (1995).

[8] Smith *et al.*, *Complete genomic sequence and analysis of 117 kb of human DNA containing the gene* BRCA1, GENOME RES., 6:1029-49 (1996).

[9] *Id.* at 1044.

P1 and BACs, it was by no means obvious to a skilled person to avoid YACs and use P1 and BACs. Our heavy reliance on P1 and BACs may even have seemed a mistake to most others in the field since it required analyzing many more smaller clones, which was regarded as being much less efficient than analyzing a few large YAC clones.

22. Another step we took that contributed to our success was our adoption of a novel hybrid selection technique, i.e., a modified version of hybrid selection.[10]

23. Generally, in hybrid selection (also called solution hybrid capture), biotinylated cloned, genomic DNA is used as a probe for hybridization in a solution of target cDNA. The hybridized probe with cDNA annealed to it is then captured by avidin on magnetic beads and the hybridized cDNA can subsequently be washed off from the beads. The cDNA is then PCR-amplified. The amplified, enriched cDNA can then be cloned and re-screened with genomic DNA to confirm the hybridization and the positive clones sequenced.

24. Specifically, in the Myriad team's novel modified version of this technique of hybrid selection, the probe was first rendered single stranded by treatment of restriction fragments of cloned genomic DNA (from the P1, BAC and cosmid clones) with exonuclease III. The largely single-stranded probe DNA was then reacted with photo-activatable biotin and UV light to generate the final probe for

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[10] *See* Harshman *et al.*, *supra* note 7; Hattier *et al.*, *Monitoring the efficacy of hybrid selection during positional cloning: the search for* BRCA1, MAMM. GENOME, 6:873-9 (1995).

hybridization. This modification minimized the competitive renaturation of probe structures during hybridization, thereby increasing hybridization efficiency and sensitivity.[11]

25. The second modification relates to target cDNA synthesis. "First, mRNA was treated with DNase prior to cDNA synthesis. This process diminished the possibility of contamination from genomic DNA. Second, cDNA synthesis involved the use of two separate primers for first and second strand synthesis. This improved the cloning efficiency of the amplified products and allowed some types of artefactual products to be identified easily." In addition, the primers incorporated into the cDNAs at the 5' and 3' ends are different, allowing immediate recognition of the orientation of the captured cDNAs.[12]

26. Overall, a total of 39 independent candidate gene fragments (CGFs) were isolated by this modified hybrid selection technique. Our modified hybrid selection proved to be the most effective method used in the search for candidate genes.[13] In fact, Dr. Roger Wiseman, a major Myriad collaborator excitedly declared that the method is "the closest thing to magic" he has seen.[14]

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[11] *See* Hattier *et al.*, *supra* note 10.

[12] *See id.*

[13] *See* Harshman *et al.*, *supra* note 7.

[14] *See The Glittering Prize*, NAT. GENET., 8:105-6 (1994).

MYRIAD COLLABORATION PIECED TOGETHER THE EVIDENCE TO ARRIVE AT THE TRUE STRUCTURE OF *BRCA1*

27. The first assembly of the *BRCA1* gene from segments of cDNA identified also presented great challenges to us. It is now known – because of our discovery – that the *BRCA1* gene has 24 exons (22 of which are coding) with a long open reading frame of 5,592 nucleotides distributed over 100 kb. Completion, for the first time, of a gene of so many exons and containing such large exons (exon 11 being more than 3.4 kb) certainly required some ingenuity and avoidance of sequence errors. As discussed above, the *BRCA1* gene could only be identified by finding mutations present in affected members of certain kindreds. If an incomplete open reading frame was mistakenly believed to be complete, segregating mutations located in the missing portion of the coding frame might have been missed and the *BRCA1* gene might have not been identified. Of course, only after the complete gene is known can its structure can be easily analyzed.

28. Indeed, four of the CGFs were alternative splice forms of *BRCA1* missing various exons. The alternative splice forms invariably resulted in truncated proteins after translation. If the Myriad Collaboration had stopped there – believing such CGFs to be represent complete open reading frames – the full length cDNA would not have been assembled, and important causal mutations might have been missed in the mutation screening of the kindreds.

29. Because of its sheer size, a full-length *BRCA1* cDNA was never identified in our screens. The full

coding structure was deduced by piecing together non-overlapping cDNA fragments. As shown in Exhibit 6, many cDNA fragments were isolated. Even minor sequence errors could have led to the obliteration of an open reading frame, and the *BRCA1* gene would not have been recognized and causal mutations would not have been discovered even in the largest and most informative kindreds. Again, only after the complete cDNA structure is known can it be reproduced easily by follow-on researchers.

BRCA1 WAS SURPRISINGLY FOUND TO NOT FOLLOW THE TRADITIONAL TUMOR SUPPRESSOR MODEL

30. Throughout the search for *BRCA1* it was widely assumed in the field that the gene we sought encoded a classic tumor suppressor. Typical tumor suppressor genes such as the previously known APC and p53 genes are involved in both familial and sporadic cancers. The following is quoted from a news report on our findings in the journal *Science*:

31. "As the name implies, tumor suppressors act as "brakes" on the conversion of a normal healthy cell into a cancerous one, and their loss or inactivation leads to cancer. Breast cancer had seemed to follow the classic model of a tumor suppressor at work: In about one half of sporadic, and all familial, cancers a stretch of chromosome 17 where researchers had been searching for *BRCA1* is lost from tumor cells, suggesting that *BRCA1* mutations play a role in both

types of cancer. But the apparent absence of *BRCA1* defects in sporadic tumors suggests otherwise."[15]

32. The article went on to quote preeminent genetic epidemiologist Neil Risch as arguing "that because the gene fails to show all the predicted features of *BRCA1*, the evidence that it really is the long-sought gene is not completely watertight."[16]

33. That no somatic mutations were found in the breast or ovarian tumor cells we initially analyzed was reported in Futreal et al.[17] Although unexpected, the lack of somatic mutations in breast or ovarian tumor cells did not detract from our evidence from kindred analysis nor our conviction that the gene we had found was indeed *BRCA1*. After the publication of the gene we called BRCA1, the scientific community went on to find mutations in this gene in many hereditary breast and ovarian cancer families, confirming our belief that is the gene we had identified was, indeed, the *BRCA1* gene.

34. This again demonstrates that the discovery of the *BRCA1* gene was by no means a trivial exercise, but a scientific accomplishment that required many inventive steps, not the least of which was to contradict the scientific dogma of the time.

Pursuant to 28 USC § 1746, I declare under penalty of perjury that the foregoing is true and correct.

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[15] Rachel Nowak, *Breast Cancer Gene Offers Surprises*, Science, 265:1796-9 (1994).

[16] *See id.*

[17] Futreal *et al.*, BRCA1 *mutations in primary breast and ovarian carcinomas*, Science, 266:120-2 (1994).

/s/ Donna M. Shattuck

Donna Shattuck, Ph.D

Executed on December 21, 2009

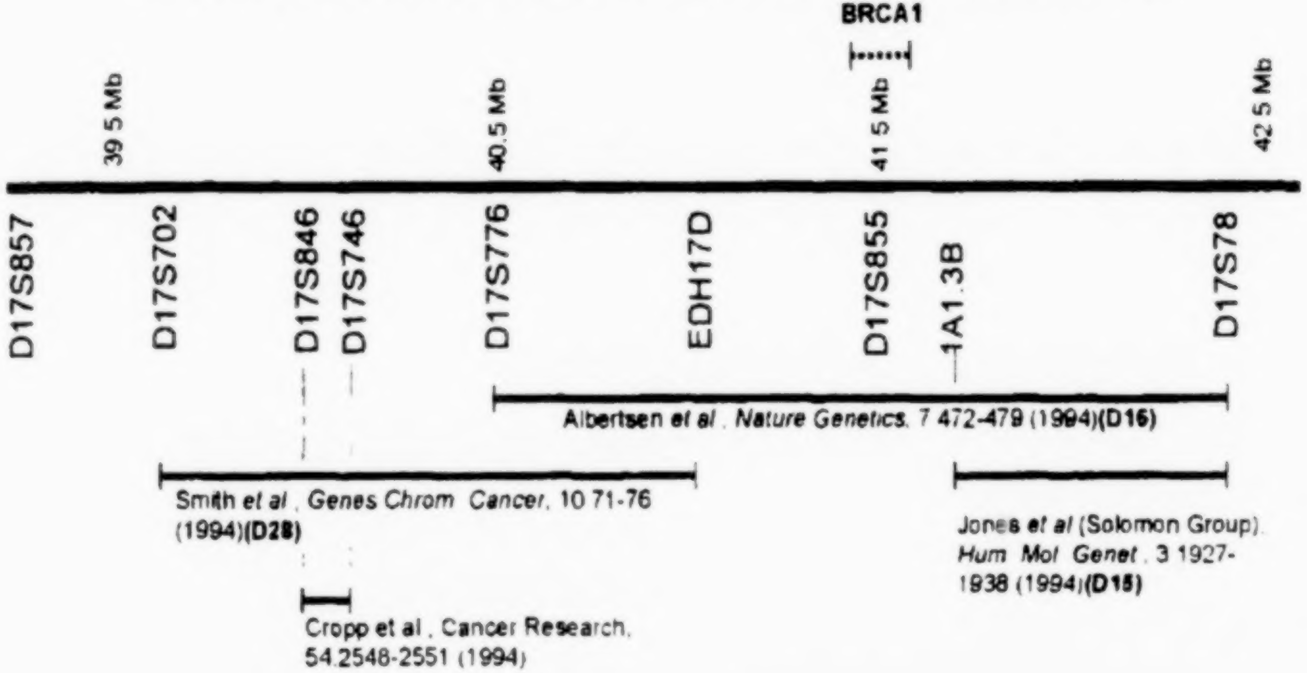
EXHIBITS 1, 2

[EXHIBITS 1, 2 OMITTED]

EXHIBIT 3

SHATTUCK DECLARATION
EXHIBIT 3

Confusion in the Art on BRCA Location


BRCA1
39 5 Mb
40.5 Mb
41 5 Mb
42 5 Mb
D17S857
D17S702
D17S846
D17S746
D17S776
EDH17D
D17S855
1A1.3B
D17S78
Albertsen *et al* . *Nature Genetics*. 7 472-479 (1994)**(D16)**
Smith *et al* , *Genes Chrom Cancer*, 10 71-76 (1994)**(D28)**
Jones *et al* (Solomon Group). *Hum Mol Genet* , 3 1927-1938 (1994)**(D15)**
Cropp et al , Cancer Research, 54,2548-2551 (1994)

Albertsen and White are co-authors on D16, D28 and the Cropp paper. Mazoyer is an author on D16 and D28

Positions July 2003 genome assembly
D17S846 chr17 40,266,349
D17S746 chr17 40,320,027

EXHIBITS 4-6

[EXHIBITS 4-6 OMITTED]

[Declaration of Mark Skolnick, filed December 23, 2009] [Caption Omitted In Printing] [Exhibit 1 Omitted]

I, Mark Skolnick, declare:

1. In 1968 I received a B.A. in economics from the University of California at Berkeley. In 1975 I received a Ph.D. in genetics from Stanford University, Stanford, California.

2. I am a founder of Myriad Genetics, Inc. ("Myriad") and currently serve as Myriad's Chief Scientific Officer and am a member of the Myriad Board of Directors. I was personally involved in the identification and characterization of the *BRCA1* and *BRCA2* genes. I am one of the named inventors in United States Patent Nos. 5,710,001, 5,747,282, & 5,753,441.

3. Myriad's discovery of BRCA1 and BRCA2 was not a trivial exercise. Nor was Myriad's molecular cloning of the genes, as described in detail in the Declaration of Donna Shattuck, the beginning of the process. Cloning was instead the culminating step in a series of endeavors on my part that lasted nearly thirty years as well as the significant effort of dozens of members of the collaborating research teams.

Connecting Demography with Genetics

4. The first scientific step in my search for the BRCA genes arose from my interest in demography, the study of human populations. The standard wisdom in the 1960's was that this was a small field that should be studied within the context of sociology or economics. However, in 1967, as a researcher at the Institute for Population and Urban Research at

the University of California at Berkeley, I had the insight that demography could be applied to genetics. I further reasoned that demographic research could be successfully merged with genetic research through the study of individuals in the context of multigenerational families, rather than the analysis of aggregate statistics of populations, such as birth rates, death rates, and migration patterns.

5. During a visit to Stanford, I met Dr. Luca L. Cavalli-Sforza, a professor in the Genetics Department at Stanford and also Director of the Institute of Genetics, in Pavia Italy. Dr. Cavalli-Sforza was one of only a handful of prominent population geneticists worldwide, and the only one who had understood the value of constructing a genealogy. Dr. Cavalli-Sforza offered me the opportunity to pursue the reconstruction of genealogies from Parma Valley, Italy to study gene flow patterns by entering the Ph.D. program at Stanford and also moving to Pavia to work with him.

6. Dr. Cavalli-Sforza had been working on this project since 1955 with little success, largely due to inadequate computing capabilities. In just over 5 years at Stanford, Parma and Pavia, I was able to integrate ideas for heuristic searches of solution spaces, which were part of the artificial intelligence program at Stanford, with the data available in Italy to create the first computerized genealogical reconstruction from parish records.

Computerizing Genealogy to Reveal the Genetics of Cancer

7. While doing my research in Pavia and Parma, I was introduced to three Mormons who had come to

establish a project to microfilm Italian parish records as they do worldwide. These interactions introduced me to the vast resources of the Utah Genealogical Society in Salt Lake City. Soon after, in 1973, I was asked by organizers of a cancer center at the University of Utah how the Mormon interest in genealogy could be used to provide a unique aspect to their evolving center. I made a proposal that was audacious at the time: reconstruct the entire Utah Mormon Genealogy from three generation family group sheets and link the genealogy to the Utah Cancer Registry which had a record for each cancer case statewide for the current generation.

8. Rather than looking for evidence of genetic predisposition by looking for vertical transmission, the standard approach, we looked for horizontal familial excess (siblings and cousins). A population based study of cancer in a genealogy was especially innovative because many researchers at the time saw cancer families as merely an interesting and unimportant anomaly. I, however, had the intuition that a population-based analysis of cancer would reveal the underlying genetics of cancer. Although this notion may seem trivial now in light of today's molecular understanding of cancer as a genetic disease, the idea was novel at the time.

9. In order to move my cancer research forward I also had to invent new methods for analysis of this database. My colleagues and I created new methods for pedigree analysis, appropriate for the complex pedigrees found in Utah, and I created a method called the Genealogical Index for analysis of the Utah Genealogy. The NIH thought that the Utah Genealogy was important and novel enough to merit

the creation of a resource so that it could be of maximal utility in the future.

Extensive Effort Was Needed to Gather Critical Data from Extensive Cancer Kindreds

10. The next step in the process which led to the discovery of BRCA1 and BRCA2 was the development of a familial cancer screening clinic, which we used extensively for the study of breast and ovarian cancer, among other familial cancers. Our approach required roughly 100 person-years of effort over two decades to study tens of thousands of members of large families with clusters of cancer. This resource was ultimately the key to our success.

Technical Innovations Helped in Finding Inherited Disease-Related Genes

11. However, a final innovative step was required in the 1970's—the concept of the use of DNA sequence polymorphism to map the human genome. We devised a technique called Restriction Fragment Length Polymorphisms (RFLPs) for genetic mapping, which was an important innovative step in the human genome project.

12. My group's activities turned to mapping and cloning disease-causing genes based on these markers. Given the difficulty of finding the genes in cancer families, we turned our attention to easier targets, to become familiar with the techniques required. We successfully mapped and cloned the gene underlying Alport Syndrome, which was known to be on the X chromosome and was one of the first genes to be found with this new technology. We also mapped the gene for neurofibromatosis, *NF1*, but were not the first to clone it because we did not have

a large enough team to compete with the groups of Ray White and Francis Collins.

Private Funding and Corporate Structure Were Critical in Finding *BRCA1* and in Ensuring the Public's Full Benefit from the Discovery

13. The *NF1* experience provided a valuable lesson to me: if I hoped to give the public the full benefit of my innovate steps and clone important genes I was going to need adequate funding and a research group large enough to compete in the laborious process of actually finding the underlying gene. So when in the fall of 1990 the linkage of a breast cancer predisposing gene, *BRCA1*, to chromosome 17 was announced, I knew that before my pioneering work in cancer genetics could help in finding the underlying gene, I was going to need a competitive team.

14. I was also keenly aware that NIH had awarded Francis Collins a massive genome center grant which would allow him to pursue cloning this gene, and that my group would most likely not be given adequate funds to compete. This in fact turned out to be true. My collaborators and I submitted a small grant proposal to pursue BRCAl, but we were turned down. We were told we didn't have the family material to be competitive, when in fact it was common knowledge that we had spent years collecting the most extraordinary breast cancer families in the world. On resubmission, we were awarded a small grant, with the funding committee stating that we should be allowed to compete even though we did not stand a chance to find the gene.

12. In other words, all the technological, informatic and pedigree innovations we had made were in danger of dying on the vine for lack of funding. Fortunately, I did not wait for NIH funding. I was acutely aware of the diagnostic importance of BRCAl. I was also aware that many other important discoveries had failed to benefit society due to the lack of an interested corporate party. I decided to create a company, Myriad Genetics, to allow our group to couple adequate molecular resources with our exceptional family data to permit us to discover BRCA1 and ensure that the public would benefit from our discovery. I am most proud of this strategy, perhaps my most important innovation.

13. Myriad Genetics was founded in May of 1991 when my interest in pursuing the discovery of the BRCA1 gene coincided with the interest of a local venture capital group in creating a company in the field of human genetics. In August 1992, we were able to attract a major pharmaceutical company as a corporate collaborator and sponsor who provided $4M in corporate research funding and who also purchased $1M in stock. We also were able to interest Dr. Walter Gilbert, who had won a Nobel Prize in 1980 for DNA sequencing and was a founder of Biogen, to join us. He brought many ideas and talents to the company, but further introduced us to an investment firm that in March of 1993 was able to raise about $8.8M in a private placement offering for Myriad. We found the first mutations in BRCA1 in the spring of 1994 and completed a second private placement financing of $9M in February of 1995. In October of 1995 we went public and in December of 1995 we discovered the BRCA2 gene.

14. Research within a company is very different from research in academia. We were acutely aware that if we were to fail to find BRCA1 we would have had great difficulty in surviving as a company and that our jobs would be lost. Rather than working for individual recognition, we worked for Myriad's recognition, and a spirit of cooperation, urgency, and comradery existed that is rare in academia. We also knew that if we found BRCA1 we would be collectively charged with bringing a diagnostic to market that had enormous significance to many women. I was acutely aware of the difficulty of changing practice in medicine, of the great changes that were required, and of the value a commercial effort could bring to helping society.

15. This is seldom recognized, but many medical discoveries languish without a corporate interest. In the United States, for example, Myriad has incurred great expense and overcome great difficulty to bring about widespread testing. In Europe, where there is no significant corporate interest, testing is infrequent largely because of the lack of a coordinated educational effort.

The strategy worked: Myriad and its collaborators were able to clone and characterize the BRCA1 and BRCA2 genes, as detailed in the Declaration of Donna Shattuck. Our team was smaller and started later than others, but the excellence of the team and our focus on the correct areas of the genome provided by our family data allowed us to work at a superior pace. Even our competitors recognized the importance of our achievement. Natalie Angier, *Fierce Competition Marked Fervid Race For Cancer Gene*, N.Y. Times, September 20, 1994, at C1 (Mary-

Claire King described it as "'beautiful' and 'lovely' and deserving of all the praise it might win.")

The Real Reason for Criticism of the BRCA Patents Is Not philosophical or Ethical, but a Simple Case of Financial Self-Interest

16. One of my first questions when this lawsuit was filed was "Why now?" Myriad discovered the *BRCA1* and *BRCA2* genes 15 and 13 years ago, respectively, and these discoveries were met with no small amount of press coverage. Further, researchers and commentators almost immediately began complaining about gene-related patents. See, e.g., D. Suslton, ¶ 33. Finally, Plaintiffs allege Myriad threatened Drs. Kazazian and Ganguly with suit over ten years ago. Why was this suit not brought at that time?

17. I believe there are two primary reasons, both of which are essentially economic. The first reason is a fairly obvious one. Plaintiffs did not have enough financial incentive in the mid- to late 1990s to bring suit because BRCA testing was not very prevalent. Only after Myriad invested over $200M raising awareness, improving education, and securing insurance coverage did the financial incentive of commercial infringement reach a level that warranted a lawsuit. Plaintiffs mention numerous labs ready to perform BRCA testing. What Plaintiffs fail to mention is that (1) these labs stand to make a substantial profit doing this kind of free-riding testing and (2) most of this testing would not be possible without Myriad's investment in patient and physician awareness and in insurance reimbursement.

18. I believe a second more subtle reason drives many opponents of gene-related patents: academic protectionism. Myriad's detractors exhibit strange behavior, which is in fact understandable when properly analyzed. They lament patenting even though they patent their discoveries. They claim our efforts are trivial, without any analysis of what led to our success. They utilize the genomic equipment that patents protect, and the patented computer equipment and processes that are part of daily scientific life. They have no trouble with the commercialization of engineering and computer science that these innovations imply. But when the commercial world enters their domain, i.e., when biotechnology and genomics companies attempt to compete for the very medical science discoveries that they believe should be the monopoly of academia, they cry foul. I believe this is because now it is their prestige and livelihood that are being challenged.

19. Indeed Myriad was the first genomics company that became successful. But the reason for the bilious attacks against us is that in the past various academic groups competed with each other on the one hand and various commercial groups competed with each other on the other hand. There had never previously been competition between a company and more than a dozen academic groups. If research stays in academia, the same groups which make the discoveries control the funding. When important research migrates to biotechnology and genomics companies in particular, the funding is generated outside of academia, and they lose control. *See*, e.g., Natalie Angier, *Fierce Competition Marked Fervid Race For Cancer Gene*, N.Y. Times, September 20, 1994, at C1 ("You get more grants, more money,

more speaking engagements at scientific conferences, better graduate students and postdoctoral fellows applying to your lab," said Dr. Barbara Weber of the University of Pennsylvania, an unsuccessful contender who said her entire laboratory had devoted every minute of the last three years to finding the gene. "It's also very glamorous. So of course I'm disappointed and frustrated.").

20. Thus what academic opponents to gene-related patents attempt to mask as ethical and constitutional issues is real nothing more than a vested interest group, academia, attempting to undermine another group, the biotechnology industry, for daring to compete in their arena.

21. It would be tragic to wipe out an entire class of patents, along with the companies that depend on them, based on this type of protectionism. This would be a serious disservice to the public and I shudder to consider how many important and vital discoveries in medicine and healthcare might never happen without the contribution of a robust biotechnology industry.

Pursuant to 28 USC § 1746, I declare under penalty of perjury that the foregoing is true and correct.

/s/ Mark Skolnick

Mark Skolnick, Ph.D

Executed on Dec. 21, 2009

EXHIBIT 1

[EXHIBIT 1 OMITTED]

[Declaration of Sean Tavtigian, filed December 23, 2009] [Caption Omitted In Printing] [Exhibits 1-5 Omitted]

I, Sean V. Tavtigian, declare:

1. In 1984 I received a B.A. with a joint major in biology and chemistry from Pomona College, Claremont, California. In 1992 I received a Ph.D. in molecular biology and biochemistry from the California Institute of Technology, Pasadena, California. I am currently an associate professor in the Department of Oncological Sciences at the University of Utah School of Medicine.

2. I was employed by Myriad Genetics, Inc. ("Myriad") between 1993 and 2002. At Myriad I held several senior positions, including Vice President, Director of Cancer Research, and Director of the (research) Sequencing and Genotyping Core at the time of my departure.

3. As a senior scientist at Myriad during the period between 1993 and 1996, I oversaw the laboratory and external collaborations components of the company's *BRCA2* positional cloning project. In particular, Dr. Alexander Kamb and I at Myriad collaborated with Dr. Jacques Simard of the University of Laval in Quebec, Canada, Dr. Johanna M. Rommens of the Hospital for Sick Children in Toronto, Canada, and Drs. Fergus Couch and Barbara L. Weber of the University of Pennsylvania in the discovery and characterization of the *BRCA2* gene in late 1995. I am one of the named inventors in United States Patent Nos. 5,709,999, 5,710,001, 5,747,282, 5,753,441, 5,837,492 & 6,033,857.

4. In discovering and characterizing *BRCA2*, Myriad and its collaborators used much the same positional cloning approach used for *BRCA1* and described in some detail in Defendant Myriad's Declaration of Donna Shattuck.

5. On December 21, 1995, at the culmination of this effort, Myriad filed patent application serial no. 08/576,559 in the United States Patent and Trademark Office disclosing the full structure of the *BRCA2* cDNA and protein.

6. A short time later the Institute of Cancer Research (ICR), one of Myriad's competitors in the search for *BRCA2* led by Michael Stratton, claimed to have discovered the *BRCA2* gene. *See* Wooster *et al.*, NATURE 378:789-92 (1995) (Exhibit 2). In this publication and its accompanying patent applications, ICR set forth what it believed to be the cDNA and protein structures for *BRCA2*.

7. As it turned out, ICR's proposed BRCA2 structure was incomplete at one end and contained a serious error at the other. More specifically, the N-terminus of what ICR called the BRCA2 protein was missing more than 280 amino acids (more than 1,000 base pairs in the cDNA and the first eight protein coding exons of the genomic structure). ICR recognized the potential for such a shortfall, stating "the N terminus of the BRCA2 protein may well be missing from the above sequence." *See* Exhibit 2, Figure 2 and legend.

8. Fully characterizing the 5' end of the *BRCA2* cDNA would have required significant additional work on the part of ICR. In arriving at the full-length *BRCA2* cDNA structure, Myriad sequenced

and pieced together numerous clones using a variety of processes, including a technique called Rapid Amplification of cDNA Ends (RACE). However, even knowing the full cDNA structure was not enough to fully characterize the gene since the structure of the resulting protein would be unknown. Though ICR apparently had the right reading frame, researchers (such as Myriad and its collaborators) still needed to definitively find the start and stop codons, a difficult task in a gene that has an open reading frame of more than 10,000 base pairs.

9. Despite these difficulties, Myriad succeeded in fully characterizing the *BRCA2* gene and submitted its full BRCA2 cDNA structure to a public database called Genbank the same day the Wooster article was published.

10. Beyond missing the N-terminus, ICR's proposed BRCA2 structure contained a much subtler and potentially more disruptive error at its C-terminus. Specifically, ICR's "*BRCA2*" structure mistakenly fused a portion of the actual *BRCA2* cDNA with a totally unrelated region of a different chromosome. This was not a rare splice variant; it was a potentially catastrophic error, *i.e.*, a chimeric artifact. As shown in Exhibits 3 & 4, respectively, ICR's proposed "BRCA2" protein structure[1] was missing the last 812 amino acids of true BRCA2[2] and

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[1] ICR's "BRCA2" protein sequence is shown in Figure 2 of the Wooster publication.

[2] True BRCA2 protein sequence herein corresponds to SEQ ID NO:2 of US Patent no. 5,837,492.

ICR's "*BRCA2*" cDNA[3] was missing the final 3,352 nucleotides of true *BRCA2*,[4] corresponding to the last ten coding exons of the gene structure. Exhibit 5 shows that, instead of being from *BRCA2*, the final 266 nucleotides of ICR's "*BRCA2*" cDNA sequence are from a region of the sequence of the X chromosome. Moreover, in contrast to their description of potential N-terminal incompleteness, the ICR's publication gives no warning about potential error at the C-terminus, strongly suggesting that the ICR team was unaware of their error (*i.e.*, the publication mentions the possibility of additional structure at the 5' end but treats the 3' end as complete and correct).

11. Imagine claiming to have found a life-saving drug, but publishing (and filing a patent application on) the correct structure of only a portion of the molecule, and mistakenly including several side groups from a completely unrelated molecule in the structure. Beyond throwing off researchers hoping to study the drug's properties, the unrelated side groups would likely detract from the drug's therapeutic efficacy and might even make the drug harmful.

12. As with the N-Terminus, Myriad correctly determined the C-terminal structure of the *BRCA2* cDNA and, in so doing, corrected ICR's errors. This

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[3] ICR's "BRCA2" cDNA sequence corresponds to SEQ ID NO:15 from PCT patent application publication WO/1997/019110.

[4] True *BRCA2* cDNA sequences herein corresponds to SEQ ID NO:1 of US Patent no. 5,837,492.

is noteworthy for two reasons. First, the process of determining the correct C-terminal structure was difficult. ICR's "BRCA2" structure was missing the final 3,352 nucleotides of true *BRCA2* as well as 10 full exons and most of an eleventh exon. More importantly, however, researchers provided with ICR's structure alone would have had no immediate reason to doubt its correctness or undertake the laborious process of determining the correct structure. For instance, as revealed from their PCT patent sequence, ICR's proposed "BRCA2" protein structure had a stop codon at the C-terminal end, suggesting that end of the protein coding sequence had been cloned. Moreover, the Wooster publication stated "Contiguity of the transcription unit was confirmed by reverse-transcription-polymerase chain reaction (RT-PCR) on cDNA and sequence analysis." Two paragraphs later, they went on to say "...including 300 bp of 3' untranslated sequence..." Together with the Figure 2, these two statements indicate that Wooster et al. thought that their sequence included a *bona fide* BRCA2 translation termination signal and were unaware that their sequence was chimeric. Further, the more than 3,000 nucleotides and 10-plus exons missing from the C-terminal end of ICR's "*BRCA2*" structure are around the size of an average genes entire cDNA.

13. While the technologies used for DNA cloning and gene sequencing are standard, the discovery and characterization of genes is by no means routine. ICR's difficulties and Myriad's successes in characterizing *BRCA2* underscore the monumental nature of the discovery and characterization of the *BRCA1* and *BRCA2* genes (*see, e.g.*, D. Mason ¶ 33, D. Parthasarathy ¶ 19). Moreover, we should keep in

mind that BRCA2 did not "have" to be a protein coding gene. Had BRCA2 been, for instance a regulatory snRNA, the cloning techniques of the mid-1990s may have been unable to find it.

14. More importantly, however, I disagree with plaintiffs' allegations that "[g]ene patents are not necessary to further scientific discovery and the development of diagnostics." *See* D. Leonard ¶ 20; *see also*, D. Sulston ¶ 38, D. Cho ¶ 17, etc. I also question plaintiffs' suggestion that academic groups (ICR is given as an example) are more generous with the genetic information they gather. *See, e.g.*, D. Sulston ¶¶ 29-33 ("From the very beginning of the Human Genome Project, most scientists and even some private companies recognized the importance of keeping the genome freely available to all.").

15. In the case of BRCA2, patents were necessary to drive forward research and also to incentivize public disclosure of genetic sequences. For example, despite the prevailing "best practices" of the day, ICR never submitted its proposed BRCA2 protein structure to a public database when it produced the Wooster publication (such submissions are routinely required by scientific journals today). The Wooster publication gave a partial BRCA2 protein sequence, but I know of no publication nor any public database submission by ICR that gives the corresponding DNA structure (which is the most important thing for a BRCA2 diagnostic test).

16. Indeed, I only discovered the true nature of ICR's errors when ICR's patent application (PCT publication no. WO/1997/019110) published with a partial cDNA structure (which was then entered automatically in Genbank). In contrast, Myriad

submitted its *BRCA2* cDNA structure to the publicly available Genbank database the day after filing its patent applications. Given Plaintiffs' allegations about patents discouraging public disclosure, it is particularly ironic that ICR's errors only came to light because the sequences were published in a patent application.

17. If Myriad had not published the full *BRCA2* cDNA structure, *see* Tavtigian *et al.*, *The Complete* BRCA2 *Gene and Mutations in Chromosome 13q-Linked Kindreds*, NATURE GENETICS 12:333-7 (1996), it is difficult to say when ICR's mistake would have been discovered or how much progress in BRCA2 research would have been delayed. The incentive provided by patents was critical in the discovery of the true structure of BRCA2.

18. In his declaration, John Sulston suggests Myriad has improperly claimed the discoveries of others. *See* D. Sulston ¶ 31. Specifically, Sulston alleges:

> Myriad used its patent applications to claim rights over the entire BRCA2 gene, including the mutations that had been identified by ICR. Myriad has since claimed proprietary rights for all diagnostic testing for the BRCA genes. One of their tests focuses on one of the mutations discovered by the ICR team that is commonly found among Ashkenazi Jews from central and eastern Europe. Thus, by having a patent on the gene as a whole, Myriad was able to claim scientific findings made by others.

19. As I discussed above, ICR's efforts fell far short of characterizing the full *BRCA2* cDNA and instead would have led BRCA researchers astray if not for Myriad's correction.

20. I also disagree with Sulston's description of the discovery of the Ashkenazi mutation. ICR may have discovered the mutation (*i.e.*, that a nucleotide change occurs at this position in the structure of *BRCA2*), it was Myriad who discovered its significance (*i.e.*, that it is a founder mutation commonly found among Ashkenazi Jews from central and eastern Europe). Neuhausen *et al.*, *Recurrent* BRCA2 *6174delT Mutations in Ashkenazi Jewish Women Affected by Breast Cancer*, NATURE GENETICS, 13:126-8 (1996). In fact, the European Patent Office, despite its more stringent absolute novelty requirements, granted Myriad a patent on the use of this mutation for determining risk in patients of Ashkenazi ancestry.

Pursuant to 28 USC § 1746, I declare under penalty of perjury that the foregoing is true and correct.

/s/ Sean Tatvigian

Sean V. Tavtigian, PhD

Executed on 12/21, 2009

EXHIBITS 1-5

[EXHIBITS 1-5 OMITTED]

[Declaration of John Doll, filed December 23, 2009] [Caption Omitted In Printing] [Exhibits 1-14 Omitted]

I, John J. Doll, hereby declare that:

1. I reside in Maryland.

2. I served as the Acting Under Secretary of Commerce for Intellectual Property and Acting Director of the United States Patent and Trademark Office during the change of administration (January 2009 to August 2009). As the Acting Under Secretary, I advised the President, the Secretary of Commerce, and the Administration about all intellectual property matters. As Acting Director, I administered the laws of granting Patents and Trademarks, and the day-to-day management of the $2.1 billion Agency for over 9,600 employees. I developed and articulated Administration positions on all Patent, Trademark and Copyright issues, both domestic and foreign while promoting strong Intellectual Property policy globally, including strategies to thwart the theft of U.S. Intellectual Property around the world. *See* Curriculum Vitae (Exhibit 1)

3. I was the Deputy Under Secretary of Commerce for Intellectual Property and Deputy Director of the United States Patent and Trademark Office (November 2008 to September 2009). In this capacity, I assisted the Under Secretary in developing and promoting Administration positions on all Patent, Trademark and Copyright issues domestically and internationally. I also served as the Chief Operating Officer in planning, measuring and improving the mission performance and

achievement of the Agency. I was responsible for maintaining and growing domestic and international leadership roles in Intellectual Property Rights policy by strengthening Intellectual Property protection. I was also responsible for providing customers with the highest levels of quality and service in all aspects of Agency operations.

4. In 2005 I was appointed as the Commissioner for Patents by the Secretary of Commerce. In this capacity from August 2005 to October 2009, I served as the Chief Operating Officer for all aspects of patent related operations, planning and policy with the mission of properly applying the patent laws and regulations of the United States in the examination of patent applications. I oversaw a budget of $1.3 billion and a staff of over 7000 employees. I was responsible for Patent's strategic planning and execution, budget formulation and execution, information technology systems, staffing, employee development, labor management relations, customer outreach, congressional relations, public advisory committee relations, and patent policy formulation.

5. Prior to my appointment as Commissioner for Patents, I served as the Acting Commissioner for Patents from April 2005 to August 2005. I was appointed by the Under Secretary of Commerce for Intellectual Property and the Director of the United States Patent and Trademark Office to perform the duties of the Commissioner for Patents until the Secretary of Commerce appointed a new Commissioner for Patents. Prior to and during this appointment, I served as the Deputy Commissioner for Patent Resources and Planning from January 2005 to August 2005. I was responsible for the

formulation and execution of the $1.3 budget as well as strategic planning for the Patent Office.

6. Before my appointment as Acting Commissioner, I served as the Director or Deputy Director of three different Patent Examination Technology Centers from August 1992 to August 2005. I was responsible for all patent examination issues in the chemistry, pharmaceutical, biotechnology and design art areas. During my tenure, from March 2004 to January 2005, I served as the Special Assistant to the Under Secretary and Director of the United States Patent and Trademark Office from March 2004 to January 2005. In this capacity, I provided technical, examination and legal advice on all Patent related issues.

7. From September 1974 to August 1992, I was a Patent Examiner, Supervisory Patent Examiner, and Quality Assurance Examiner. I examined and supervised the examination of patent applications encompassing pharmaceuticals, herbicides, pesticides, dyestuffs, inorganic chemistry, hydrometallurgy, zeolite catalysts, buckministerfullerenes, proteins, and peptides.

8. I have been honored on multiple occasions for my service at the United States Patent and Trademark Office. Among my honors, I received the Department of Commerce Bronze Medal for examination and supervisory accomplishments; a second Bronze Medal for the implementation of Patent Application Location and Monitoring (PALM) system; a Department of Commerce Silver Medal for the development of automated examiner office action tools; the Vice Presidential Hammer Award for establishing the Biotechnology Customer

Partnership; a Department of Commerce Gold Medal for implementation of the Image File Wrapper system.

9. I received my Master of Science in Physical Chemistry in 1974 from The Pennsylvania State University. I received my Bachelor of Science in Chemistry and Physics in 1971 from Bowling Green State University.

10. In preparing this Declaration, I reviewed and considered the Plaintiffs' Statement of Material Facts ("SMF"); Plaintiffs' Memorandum of Law in Support of Motion for Summary Judgment ("Memo"); Dr, John Sulston's and Dr. Myles Jackson's Declarations; the Utility Examination Guidelines (66 Fed. Reg. 1092 (January 5, 2001)); United States Patent Nos. 5,747,282 ("the '282 patent"); 5,837,492 ("the '492 patent"); 5,693,473 ("the '474 patent"); 5,710,001 ("the '001 patent"); 5,753,441 ("the '441 patent"); 6,033,857 ("the '857 patent"); 5,709,999 ("the '999 patent"), (collectively "Myriad patents").

THE USPTO ADMINISTERS THE LAWS ENACTED BY CONGRESS

11. The U.S. Patent and Trademark Office ("USPTO" or the "Office") is an administrative agency charged with examining applications for patent. The USPTO issues a patent if the application meets the statutory requirements of Title 35 United States Code, Title 37 Code of Federal Regulations and the procedures of the Manual of Patent Examining Procedure ("MPEP"). The USPTO must apply the laws Congress has enacted and the Federal Circuit and the Supreme Court have interpreted.

12. On October 17, 1994, Commissioner Bruce Lehman conducted a public hearing in San Diego on the patenting of biological inventions before the USPTO. Public Hearing on the Patenting of Biotechnological Inventions before the United States Patent and Trademark Office (Oct. 17, 1994), located at http://www.uspto.gov/web/offices/com/hearings/biotech/biotrans.html (Exhibit 2). The purpose of the public hearing was to obtain input from the industry in connection with the Office's review of its examining procedures to ensure that examination was of sufficiently high quality, and that the USPTO was responsive to the industry's needs.

13. The recurrent theme of the testimony received from industry representatives at that hearing, sometimes referred to as "the San Diego Massacre," was that the USPTO applied a more stringent and uneven standard for biotechnology inventions, and that we were "killing the industry" by not issuing patents for biotechnology inventions. Mostly, the complaints related to uneven examination standards, peer review rather than legal review of patent applications, and that a special higher standard for patentability (in particular, utility) was being applied to biotechnology inventions.

14. In response, the USPTO issued utility examination Guidelines to address the concerns aired at the public hearing. Utility Examination Guidelines, 60 Fed. Reg. 36263 (1995) (reproduced in MPEP § 706.03(a)(1) (July 1998) (hereafter "1995 Utility Guidelines")) (Exhibit 3). The Guidelines are not law or substantive rules. Rather, the Guidelines define the procedures to be followed by Office personnel in their review of patent applications for

compliance with 35 USC § 101. The legal analysis supporting the Guidelines articulated the basis for the procedures that were established.

15. In February of 1995, I was asked to be the Director of the Patent Examination Technology Center 1800, which examined patent applications claiming biotechnological inventions. Shortly after taking the position, I was told of a backlog of unexamined applications in Group 1800 relating to "ESTs" ("expressed sequence tags"). An EST is a short fragment of a cDNA that represents a portion of an expressed gene. Patenting "anonymous" EST fragments was controversial. There was a concern that patents on ESTs without knowledge of the function of the gene, could potentially dominate or preclude a patent to those who later deciphered the structure of the full length gene and the function of the gene. The Technology Center was holding the EST applications and not examining them since they were unsure how to properly apply the patent laws and regulations to EST applications claiming, sometimes, thousands of ESTs in a single application. Thus, there was a moratorium on examination of these applications.[1]

16. After I was briefed on the EST applications, it was apparent that the examination of EST

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[1] Plaintiffs' expert, Jackson, is incorrect when he states that ESTs were easy to patent in the mid-1990s (Jackson Declaration, p. 11, n.13). Patents on ESTs were not issued during this time period, and ultimately, patentability of ESTs without knowledge of function of the corresponding gene product was denied by the Federal Circuit (In re Fisher, 421 F.3d 1365 (1995)).

applications presented some unique examination issues. I began discussions with the Office of the General Counsel and the Solicitor's Office to determine the appropriate examination procedures for EST applications and to get the examination of these applications started.

17. A team from the Office of the General Counsel, including the Solicitor's Office, and the Technology Center convened and studied the law on patent eligibility of DNA molecules and the criteria that would be required to address the concerns about ESTs. The results showed that utility was the main issue that needed to be addressed. The USPTO also consulted with various groups, including Pharmaceutical Research and Manufacturers of America ("PhRMA") and Biotechnology Industry Organization ("BIO"), and agencies, including the National Institutes of Health ("NIH"), the Department of Commerce ("DOC"), and the Office of Management and Budget ("OMB"), to develop a framework for examining DNA EST patent applications.

18. Through this process, the USPTO refined its procedures for examining all inventions including biotechnology inventions to require a specific, credible and substantial utility for DNA molecules claimed. This was done to ensure that patents did not issue on DNA molecules without a proper disclosure of utility satisfying 35 USC § 101. These criteria were published in the revised Guidelines. Revised Interim Utility Examination Guidelines, 64 Fed. Reg. 71440 (December 21, 1999) (hereinafter "1999 Interim Guidelines") (Exhibit 4). The Utility Examination Guidelines that were released in 2001

(Utility Examination Guidelines, 66 Fed. Reg. 1092 (January 5, 2001) (hereinafter "2001 Utility Guidelines") (Exhibit 5)) were based on the 1999 Interim Guidelines. The USPTO incorporated these Guidelines into the MPEP. U.S. Pat. & Trademark Off., MPEP § 2107 (8th ed. 2001) (Exhibit 6).

19. In order to explain our position regarding the examination of patent applications relating to DNA molecules to the public, I worked with the Office of Public Affairs, the Office of the General Counsel including the Solicitor's Office, and the Technology Center, and wrote an article published in Science. Doll, J.J., 1998, "The Patenting of DNA" *Science* 280: 689-690 (Exhibit 7).

20. During the evolution of the Examination Guidelines, several of the plaintiffs and plaintiffs' experts in this action participated in the commentary and expressed their concern with the possible impact of patents granted for DNA-related inventions, particularly with respect to ESTs. [Association for Molecular Pathology, Debra Leonard, Wayne W. Grody, Mark E. Sobol, The American College of Medical Genetics, David H. Ledbetter]. A number of the participants commended the USPTO's approach since it addressed their major concern in that the Guidelines would prevent the patenting of DNA molecules where the function of the gene product was unknown. *See* Letter from R. Rodney Howell, President, American College of Molecular Genetics to Commissioner, USPTO (March 20, 2000), *available at* http://www.uspto.gov/web/offices/com/sol/comments/ utilguide/acmg.pdf (Exhibit 8); Letter from Debra G.B. Leonard, President, Association for Molecular Pathology to Commissioner, USPTO

(March 17, 2000), (hereinafter "AMP Letter"), *available at* http://www.uspto.gov/web/offices/com/sol/comments/utilguide/amp.pdf (Exhibit 9).

21. The only remaining concern expressed was whether patents in this area were in the public interest (AMP Letter ¶ 3) – an issue mirrored in the plaintiffs' complaint. *See* Plaintiffs' Complaint, ¶¶ 2, 81-101. This is a policy issue that can only be addressed by Congress, not the courts and not the USPTO.

22. I will now explain what criteria were used to assess patentability of biotechnological inventions, in particular for DNA molecules, and how the USPTO applied them.

ISOLATED DNA MOLECULES ARE PATENT ELIGIBLE SUBJECT MATTER

23. New areas of technology do not create the need for a whole new specialized area of patent law. The patent statutes and regulations are the same for all inventions regardless of whether they are genes, semiconductors, computers, pesticides or doorbells. Neither the Congress nor the courts have indicated that patent law should be changed with the introduction of genetic technology or any other specific technologies. Had Congress wanted the USPTO to apply different standards to different technologies, I believe Congress would have expressly done so.

24. The same patentability analysis has always been applied by USPTO regardless of the technology. The laws have consistently remained the same through every new class of inventive effort because

they established a patent regime that has worked well.

25. As I pointed out in my Science article, in many ways, Plaintiffs' arguments resemble those voiced 30 to 40 years ago when polymer chemistry was an emerging technology. At that time, it was argued that patents on the building blocks of basic polymers would devastate the industry. In fact, no such disaster occurred. For example, the issuance in 1965 of a basic patent broadly claiming a vulcanizable copolymer of aliphatic mono-olefins and unsaturated bridged-ring hydrocarbons (*i.e.*, ethylene-propylene-diene monomer ("EPDM") rubber) did not preclude the later issuing of patents to different inventors for several copolymers of this type (Exhibit 7 ¶ 3-4).

26. Isolated or purified DNA molecules are chemical compositions that are eligible for patent protection under 35 USC § 101 as compositions of matter. They are not naturally occurring substances and they are not just information.

27. Isolated or purified DNA molecules are chemical compositions that possess physical, chemical and structural properties that differ from their naturally occurring counterpart genes. In their natural state, genes are chemically bonded into long strands of nucleotides that make up chromosomes. Genes do not float around in cells as separate entities; one cannot simply reach into a cell and pull a gene out of the body. It requires research and discovery to identify, isolate or synthesize and sequence a gene from the vast run of nucleotides on a chromosome. There is no roadmap as to where the genes are located on a chromosome or what function the gene products have.

28. Isolating or purifying a gene is not simply copying its information into another format. The isolated DNA is chemically, physically and structurally different from the gene in the body. Just like any other chemical composition, DNA contains various groupings of atoms. DNA specifically contains carbon, hydrogen, nitrogen, oxygen and phosphorous atoms that are bonded in a manner that determines its properties, just as the properties of any chemical composition are determined by the atoms that comprise it and the manner in which they are bonded. Even if the information in an isolated DNA molecule is the same as its genomic counterpart, it would not preclude the isolated DNA from being patent eligible subject matter.

29. A critical aspect of any chemical compound is its inherent chemical, physical and structural properties, such as chemical reactivity, catalytic properties, and biological interactions. This is also true of DNA. An isolated DNA has a different number of atoms of various elements that are bonded in a manner that is distinct from the gene sequence found in the body. As a result, an isolated DNA has properties, functions and utilities that the gene in the body does not have. For example, the isolated DNA, but not the naturally occurring gene, can be used as a diagnostic probe, molecular marker, or source primer.

30. The Plaintiffs contend that genetic sequences are information and should not be patentable. SMF ¶¶ 48-49, 59, 65, 96, 114. The Plaintiffs fail to see that the inherent information contained in a composition of matter is not what is patented in a composition of matter claim. What is patented is the

composition of matter itself and the patent excludes others from making using selling or importing the patented invention which includes all of chemical, physical, structural and informational properties for that specific composition of matter.

31. A DNA molecule is a chemical composition that is composed of structural units called nucleotides. A nucleotide consists of an phosphate, a deoxyribose sugar, and one of four bases: Adenine (A), Thymine (T), Cytosine (C), and Guanine (G). The letters are just assigned to the nucleotides so that a DNA molecule may be more easily depicted. This system is analogous to the chemical formulas used for describing other chemical compounds. For example, the chemical formula for water is H_2O, where "H" represents a hydrogen atom, "2" represents the number of hydrogen atoms present in the compound, and "O" represents an oxygen atom. The recitation of a chemical formula in a claim does not mean that the inventor is patenting the chemical formula – it is the chemical composition of matter is being patented. So analogously, when a nucleotide sequence is recited in a claim, the inventor is not claiming the sequence, but the DNA molecule as a chemical composition.

32. As the Plaintiffs acknowledge, cDNAs are not natural forms of DNA that are found in the human body. They are synthesized by reverse transcribing mRNA in a laboratory. SMF ¶ 62. They are chemical compositions of matter that are chemically, physically and structurally different from naturally occurring genes.

33. For example, cDNAs are not the same as the gene sequence in the body – they lack the introns

that are present in the naturally occurring gene. Even if we assume for argument's sake that a sequence of a cDNA was identical to a DNA sequence in the body, the cDNA would be a very small part of a chromosome's huge string of nucleotides present in the body, and thus would have totally different properties than any naturally occurring composition of matter. Thus, Plaintiffs are wrong when they claim that "[t]he sequence of a cDNA ... is identical to that in the body." SMF ¶¶ 62, 63.

34. Plaintiffs incorrectly conclude that genes and their mutations are unpatentable because they are manifestations of laws of nature. SMF ¶¶ 73, 81. Every composition of matter ever patented can be said to embody the inherent laws of nature dictated by the chemical, physical and structural properties of that particular chemical combination of atoms – this does not render those compositions unpatentable. Determining specifically which nucleotides on a chromosome relate to a gene of a specific function and which variations of that gene indicate a predisposition to a specific disease is certainly a discovery which is patent eligible under § 101. Claims covering isolated DNA molecules with a specific, substantial and credible utility, and methods using them to screen, analyze, or diagnose are patent eligible.

35. The USPTO has examined countless applications using the standards I discussed. I searched the USPTO database and found that over the past 29 years, the USPTO has issued some 2,645 patents claiming "isolated DNA." http://patft.uspto.gov/netahtml/PTO/search-adv.htm (search query ACLM/"isolated DNA") (Exhibit 10).

Seven of these patents are the Myriad Patents challenged by the plaintiffs.

36. Moreover, I am aware of several patents that are related to genes implicated in different diseases and that have been issued to some of the plaintiffs in this case - Dr. Haig Kazazian 5,407,796, ("Cystic Fibrosis Mutation Cluster")) (Exhibit 11); Dr. Stephen T. Warren (Patents 6,107,025 and 6,180,337 (both entitled "Diagnosis of the Fragile X Syndrome")) (Exhibit 12 and 13); and Dr. David H. Ledbetter (Patent 6,143,504 ("Methods and Compositions for the Diagnosis of Fragile X Syndrome")) (Exhibit 14).

MYRIAD'S BRCA GENE PATENT CLAIMS MEET THE STANDARDS OF § 101

37. I believe that all of the Myriad patent claims in question here meet the requirements for patent eligibility reflected in 35 USC § 101, the Regulations, Guidelines, and the USPTO's practice and procedures set forth in the Manual of Patent Examining Procedure (MPEP) for composition of matter and method claims.

38. Challenged claim 1 of the '473 patent, claims 1 and 2 of the '282 patent, and claims 1,6 and 7 of the '492 patent recite isolated BRCA1/2 DNA molecules. Chemical compositions of matter were patented in these patents, not functionality or information.

39. The utility of the BRCA1/2 composition of matter claims are specific, credible and substantial, thus meeting the elevated utility standard set forth in the 2001 Utility Guidelines. The Myriad patents describe the function of the gene products and discovered the significance of the mutations; these

patents are different from the EST patents I discussed earlier.

40. The language of Claim 1 of patents '999, '001, and '441 and Claims 1 and 2 of patent '857 is typical for method claims found throughout thousands of patents for detecting or screening a sample against a normal sample and meet all of the statutory requirements for patentability.

41. The language of Claim 2 of patents '857, patent appears to be the same as thousands of other patented diagnostic claims and meet all of the statutory requirements for patentability.

42. The language of Claim 20 of '282 patent is common for method claims found in thousands of patents for screening drugs using cell culture and meet all of the statutory requirements for patentability.

43. Plaintiffs allege that "[s]ome of Myriad's patents cover mutations that were found by other scientists." SMF ¶ 98. If this is true and if Myriad is not the first true inventor of patented subject matter, there are established procedures to address this concern.[2] However, this is irrelevant to the issue of patent eligibility of the subject matter claimed.

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[2] Which party first invented the commonly claimed invention can be determined through an interference proceeding under 35 USC § 135(a).

PATENTS PROMOTE RESEARCH AND COMMERCIALIZATION

44. The Plaintiffs express concern that the right to exclude others from using the patented invention will limit the number of other laboratories that can provide the same services as Myriad. SMF ¶¶ 10-12, 87, 139. What the Plaintiffs fail to acknowledge, however, is that the patentee's right to exclude is limited in time, after which the patented invention is donated to the public to freely use. The Constitution expressly permits this quid pro quo contract with the government which the patent system ensures.[3]

45. Patents encourage the sharing of inventions and discoveries by discouraging trade secrets. Without patents and the protections they grant, the world would have less information and many fewer life saving drugs and therapies. More people would have died and there would be less information to use as the basis for future research.

46. Without patents which allow researchers to profit from their discoveries, many discoveries would not have been made. Public funding alone simply could not fund all the research and commercialization that the combination of public and private funding currently accomplishes. Many of the life saving inventions that the world now enjoys would never have been discovered or commercialized

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[3] U.S. Constitution, Article 1, Section 8, Clause 8 clearly states "The Congress shall have the Power to promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries."

if it were not for the potential profits afforded by the temporary exclusive rights granted by the patent system. Undoubtedly, many researchers would not have embarked on their research in the first place because they could not afford it or did not have a place to conduct the desired research. Also, the information disclosed in patents provides other researchers with the knowledge and a new starting point to begin research based on the information disclosed in the patent. The discovery and characterization of a gene permits a multitude of other patent possibilities, e.g., diagnostic probes, methods of activating or deactivating, gene splicing, gene replacement therapies, and discovering genes within genes.

47. Contrary to the clinicians and physicians who complain that gene patents interfere with an individual's ability to make informed health decisions (SMF ¶¶ 7-9, 13, 14, 17, 82, 83), gene patents give people options that may not have been available if not for the exclusive rights granted by patents allowing researchers and companies the opportunity to recover the research and development ("R&D") cost and to possibly return a profit for corporations, shareholders and venture capitalists. Many of the life saving inventions that the world now enjoys would never have been discovered or commercialized if it were not for the exclusive rights granted by the patent system.

48. Myriad might not have spent the monies on the R&D that provided the BRCA1 and BRCA2 information to the world if it were not for the exclusive rights granted by the patent system and the possibility of recovering their R&D costs and to

return a profit for their shareholders and venture capitalists. There is nothing of record to suggest that, without Myriad's R&D, the world would have the benefit of the life saving advancements claimed and disclosed in their patents.

49. The Plaintiffs also argue that DNA molecules should not be patentable because DNA patents "can serve as a disincentive to innovation in molecular testing and medicine because they deny access to a vital baseline of genomic information that cannot be 'invented around.'" SMF ¶¶ 1, 3, 50, 114, 175-192. The Supreme Court captured the overbreadth of this criticism in *Diamond v. Chakrabarty*, 447 U.S. 303, 317 (1980), "[t]he grant or denial of patents ... is not likely to put an end to genetic research ... patentability will not deter the scientific mind from probing into the unknown ... Whether respondent's claims are patentable may determine whether research efforts are accelerated by the hope of reward or slowed by want of incentives, that is all." Although the new discoveries resulting from the R&D of "inventing around" are a benefit of the patent system, the ability to invent around an invention is not a statutory patentability requirement. That an invention is fundamental to human nature and scientific inquiry does not preclude it from patentability. This issue is not part of the calculus of the patent statutes established by Congress and repeatedly interpreted by the Courts or the guidelines set forth by the USPTO.

50. Many women and men have benefited from the Myriad patented compounds and methods. These benefits probably would not have come about if it were not for Myriad's R&D which is highly likely to

have been supported by the profits from their patents. Myriad is using the patent system for exactly what it was intended - to exclude others from making, using, selling and importing their patented invention(s) for a limited time, after which the invention becomes available to the public to freely use.

51. Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct.

/s/ John Doll

John Doll

Executed on December 22, 2009

EXHIBITS 1-14

[EXHIBITS 1-14 OMITTED]

[Declaration of William Rusconi, filed December 23, 2009] [Caption Omitted In Printing]

I, William Rusconi, declare:

1. In 1983 I received a B.S. in molecular biology, with minors in German, chemistry and psychology, from Vanderbilt University, Nashville, Tennessee. In 1994 I received an M.B.A. (MM) with majors in marketing, finance, and international business, while making the Dean's List in 1993-1994, from the Kellogg Graduate School of Management at Northwestern University, Evanston, Illinois. In 1982 I was a genetic engineering intern with the U.S. Environmental Protection Agency-IERL, Toxics Staff, in Cincinnati, Ohio.

2. I am Senior Vice President of Marketing at Myriad Genetic Laboratories, Inc. ("Myriad"). I also oversee Myriad's Managed Care department. These departments are responsible for Myriad's patient and physician awareness and education efforts and for Myriad's ongoing relationships with insurance payors.

3. Myriad has undertaken extensive efforts and incurred significant expense for over 13 years to secure insurance reimbursement for Myriad's BRAC*Analysis*® test for as many appropriate patients as possible. Myriad has nearly a dozen full-time staff members whose sole responsibility is securing criteria, medical policy, and coverage with the numerous insurance payors in the United States. This process includes educating payors on hereditary cancer syndromes and professional society guidelines for genetic testing.

4. After considerable time and expense, this effort has borne substantial fruit, much to the benefit of patients. Myriad has received reimbursement for its BRAC*Analysis*® test for patients from over 2,600 different health insurance payors from every state. Myriad is a "participating provider" under 25 state Medicaid programs. These payors encompass over 80,000 distinct health insurance plan groups covering more than 130 million lives. Additionally, Myriad's BRAC*Analysis*® test is reimbursed under Medicare.

5. Until Myriad is approved by each state as a "participating provider," we cannot offer testing to that state's Medicaid patients. Myriad has been pursuing Medicaid coverage for years and has secured "participating provider" status in 25 states. Unfortunately, while Myriad continues its efforts to secure Medicaid coverage in all states, Myriad has not yet been granted "participating provider" status in some states, which may create gaps in coverage for some patients.

6. However, Myriad provides free testing to indigent patients. For example, Myriad has a financial assistance program that allows for free testing for patients meeting specific criteria. Further, in 2009 Myriad began granting free BRAC*Analysis*® testing to The Cancer Resource Foundation (CRF) to be distributed to needy Massachusetts patients at CRF's discretion (i.e., based upon medical and financial criteria of CRF's choice). This is the type of program under which MassHealth patients such as Plaintiff Ceriani have an opportunity to receive BRAC*Analysis*® testing at no cost.

7. Since identifying and characterizing the BRCA genes, Myriad has spent over $200 million raising patient and physician awareness about hereditary breast and ovarian cancer and promoting BRCA testing.

8. For physicians, Myriad: provides web-based, print and in-person education (including professional society meetings, regional education events, etc.); contributes to numerous journal publications that help in hereditary breast and ovarian cancer ("HBOC") education and awareness; has produced thousands of hours of CME material on HBOC; has produced office-based tools to help doctors to identify and counsel patients; employs regional medical specialists who assist physicians in understanding HBOC testing and their test results; and maintains a detailed website with extensive resources for doctors and other health care professionals.

9. For patients, Myriad: has spent over $20 million in the last three years alone on a mass-media awareness campaign; produces and distributes patient education videos and written materials explaining HBOC and genetic testing; supports advocacy organizations such as Susan G. Komen for the Cure, Be Bright Pink, National Ovarian Cancer Coalition, Young Survival, Y-ME, etc.; provides clinical support to providers and patients, including a hotline, to help patients understand HBOC testing; and maintains a detailed website with extensive resources for patients and their families.

Pursuant to 28 USC § 1746, I declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge and belief.

/s/ William E. Rusconi

William E. Rusconi

Executed on 22 December, 2009

[Declaration of John Franklin Sandbach, filed December 23, 2009] [Caption Omitted In Printing]

I, John Franklin Sandbach, declare under penalty of perjury:

1. I am board certified in hematology and medical oncology. I have treated patients as a partner at Texas Oncology, P.A. since 1994. I have served on the Board of Texas Oncology since 2002.

2. In 1967 I received a B.S. and in 1971 I received an MD, both from the University of Kentucky. From 1971-1972 I was an intern in the internal medicine department at the University of North Carolina, from 1972-1973 I was an internal medicine resident, and from 1973-1974 I was a fellow in hematology at North Carolina Memorial Hospital. A full copy of my *curriculum vitae*, including a list of publications, is attached as Exhibit 1.

3. I recently headed two clinical research studies into hereditary breast and ovarian cancer (HBOC) syndrome and the BRCA genes. I was aware that Myriad's patent rights covered certain aspects of the BRCA genes.

4. In one study I looked at *BRCA1/BRCA2* testing in a traditionally understudied setting: community oncology clinics. We found that mutation rates and demographics in these clinics mirror those found nationally. We also found a significantly higher than expected proportion of patients whose family history warranted *BRCA1/BRCA2* testing. We concluded that community oncology practices can effectively identify and test women who are at risk

for *BRCA1/2* mutations, but to do so these practices must implement an effective screening method to identify patients, address patient reasons for declining testing, provide comprehensive pre- and post-test consultation, and provide appropriate patient management options.

5. In another study, which is ongoing, I am looking at the rate of *BRCA1/BRCA2* mutations in patients with "triple-negative" breast cancer (*i.e.*, tumors show an absence of estrogen, progesterone, and HER2/neu receptors). In this study we are evaluating the hypotheses that patients who present with triple-negative breast cancer have a significantly elevated likelihood of carrying a mutation in *BRCA1/2* and that this elevated likelihood is also prevalent among the sub-set of triple-negative patients that do not have a family history of breast or ovarian cancer. If triple-negative breast cancers are enriched for *BRCA1* mutations, they may be more likely to respond to specific therapy such as cisplatin and PARP inhibitors, thus potentially increasing the chance for meaningful responses to therapy or improved cure rates in the adjuvant setting. Because patients with *BRCA1* mutations are also at risk for second breast cancers and ovarian cancers, preventative measures and screening are crucial to early detection and improved overall survival. Therefore identifying patients with elevated likelihood for carrying a *BRCA1/2* mutation is a high priority. If the hypotheses listed above are true, this would comprise compelling evidence that genetic testing for *BRCA1/2* mutations in patients with triple-negative breast tumors would be indicated, providing an opportunity for live-saving interventions particularly in individuals whose

family history would not have identified them as being at sufficiently high risk for testing. Patients meeting the criteria for inclusion in this study are receiving *BRCA1/BRCA2* testing at Myriad at no cost.

7. Neither the patents at issue in this suit nor Myriad Genetics, Inc. have in any way hampered my research. To the contrary, in both of these research endeavors I collaborated with and enjoyed the contribution of Myriad researchers.

Pursuant to 28 USC § 1746, I declare under penalty of perjury that the foregoing is true and correct.

/s/ John Franklin Sandbach

John Franklin Sandbach, MD

Executed on December 22, 2009

EXHIBIT 1

John Franklin Sandbach, M.D.

3606 Windsor Road
Austin, Texas 78703 Phone: (512) 474-7802

Texas Oncology Cancer Center
6204 Balcones Drive
Austin, Texas 78731
Phone: (512) 427-9400
Fax: (512) 302-1408

Personal History

DATE OF BIRTH:	August 16, 1946
PLACE OF BIRTH:	Enid, Oklahoma
MARITAL STATUS:	Married
NAME OF SPOUSE:	Gene Anne Cox Sandbach

CHILDREN:
Emily Jane Sandbach, May 24, 1973
John Cox Sandbach, February 5, 1976
Anna Katherine Sandbach, December 12, 1987

Education and Training History

UNDERGRADUATE:

University of Kentucky
Lexington, Kentucky, 1964-1967

MEDICAL:

University of Kentucky, M.D.
Lexington, Kentucky, 1967-1971

INTERNSHIP:

North Carolina Memorial Hospital
Straight Medicine
Chapel Hill, N.C., 1971-1972

RESIDENCY:

North Carolina Memorial Hospital
Internal Medicine, Admitting Resident
Chapel Hill, N.C., 1972-1973

FELLOWSHIPS:

North Carolina Memorial Hospital
Hematology/Oncology
Chapel Hill, N.C., 1973-1974

Certification

Diplomate, National Board of Medical Examiners, 1972
Diplomate, American Board of Internal Medicine, 1974
Board Certified, American Board of Internal Medicine, Hematology, 1977
Board Certified, American Board of Internal Medicine, Medical Oncology, 1979

Licensure

Texas Medical License (E-8517)
Colorado Medical License (34454) (inactive)
North Carolina Medical License (18140) (inactive)
Virginia Medical License (26553) (inactive)
Kentucky Medical License (16306) (inactive)
Drug Enforcement Administration (AS7585360)
Texas Department of Public Safety (00030785)
National Cancer Institute – Investigational Drug (07164)

Work History

1971 – 1975 – Fellowship at UNC
1976 – 1977 – USAF @ Andrews Air Force Base in Maryland
1977 – 1995 – Austin Diagnostic Clinic
1994 – Present – Texas Oncology, P.A.

Appointments

MEDICAL STAFF:

North Carolina Memorial Hospital. Chapel Hill, N.C., 1973-1975

Malcolm Grow Medical Center
Andrews Air Force Base, Maryland
Hematologist/Oncologist, 1975-1976

The Austin Diagnostic Clinic, Austin, Texas
Private Practice of Hematology/Oncology, 1977 to 1995
Chief of Hematology/Oncology Section, 1986-1988

Holy Cross Hospital, Chief of Medicine
Austin, Texas, 1978-1979

The Austin Diagnostic Clinic
Board of Directors, 1989-1994

Texas Oncology, P.A., Partner
Austin, Texas, 1994 to present

CLINICAL RESEARCH:

Texas Cancer Center, Director of Research, Austin, Texas 1992 to 1999

Physician Reliance Network Research, General Medical Oncology, Program Director 1996-1998

U.S. Oncology Research. Committee Co-Chair, General Medical Oncology Research Committee, 1999-2002

U.S. Oncology Research, Committee Vice-Chairman, General Medical Research Committee, 2002-present

Texas Oncology P.A., Board of Directors, April 2002 – present

SCIENTIFIC:

Consultant, Handbook of Nonprescription Drugs, Fifth Edition

American Pharmaceutical Association, 1977

Consultant, Scientific Publications Committee of Texas Medicine, published by the Texas Medical Association, 1980 to 1996

Consultant, Archives of Internal Medicine, Editorial Review Board, 1985 to 1994

Editorial Board, Investigational New Drugs, 1986 to 1996

American Society of Clinical Oncology Chemotherapy Sensitivity and Resistance Assay Working Group, 2003

Medical Director Genetics Program US Oncology 2009 – present

MEDICAL:

Austin Comprehensive Hospice Program
Board of Directors, 1979 – 1984, 1993 – 1998,
Hospice Austin; Physician Advisory
Committee, 2000 to present

Medical Imaging Center of Austin
Board of Directors, 1979 – 1984
Chairman of the Board, 1985 – 1988

United Action for the Elderly, Austin, Texas
Board of Directors, 1986 – 1987

PacifiCare of Texas/Austin
Chairman, Utilization Review Committee, 1988 – 1989

The Austin Diagnostic Clinic Research Foundation
Board of Directors, 1986 – 1990
Vice Chairman, 1989 – 1990

St. David's Community Hospital, Austin, Texas
Chairman, Pharmacy and Therapeutics Committee, 1984 – 1986

Texas Oncology, P.A.
Medical Oncology Quality Committee, 1996 – present

Texas Oncology, P.A.
Board of Directors, 2002 – present

Military History

Malcolm Grow Medical Center
Major, Andrews AFB, Maryland
Hematology/Oncology Division, 1975 – 1977

Teaching Assignments

The University of Texas Health Science Center at San Antonio
Associate Professor of Medicine, 1982 – 2002

Honors and Awards

Roche Medical Scholarship, 1970-1971
Alpha Omega Alpha, 1971
Outstanding Intern Award, 1972

Clinical Cancer Training Grant; Public Health Service Grant
(T12-CA-98114-90) 1973 – 1975
Health Care Hero-Austin Business Journal, 2006

Professional Organizations/Committees

Alpha Epsilon Delta, 1966

Alpha Omega Alpha, 1971

USAF Reserve – Commissioned Officer, 1972

Associate – American College of Physicians, 1973 – 1975

Southwestern Oncology Group, 1982 – 2000

American Medical Association

Texas Medical Association

American Cancer Society

American Society of Clinical Oncology

Southwestern Oncology Group Breast Committee, 1983 – 1990

American Society of Clinical Oncology Education Committee, 1983 – 1984

American Society of Clinical Oncology Scientific Program Committee, 1984 – 1985

American Society of Clinical Oncology Nominations Committee, 1986

Austin Comprehensive Hospice Program, Chairman of the Board, 1979 – 1984; member, Board of Directors, 1993 – 1998

Hospice Austin Foundation, 2006-Present

Privileges

ACTIVE STAFF:

Brackenridge Hospital, Austin, Texas
Seton Medical Center, Austin, Texas
Seton Northwest Hospital, Austin, Texas
St. David's Hospital, Austin, Texas
Heart Hospital, Austin, Texas
South Austin Medical Center
North Austin Medical Center

Presentations

Sandbach, J.: Hospice Care, Central Texas Cancer Symposium, Austin, Texas, March 1980

Sandbach, J.: Faculty, 3rd Annual Breast Cancer Symposium, University of Texas Health Science Center, San Antonio, Texas, November 1980.

Sandbach, J.: Direct Cloning of Human Breast Cancer in Soft Agar, Plenary Session, American Society of Clinical Oncology and American Association of Cancer Research, 1981.

Sandbach, J.: Guest speaker, Technocracy Ethics: "Live or Let Die" at St. David's Community Hospital. Technocracy Ethics Lecture Series, September 1987.

Publications and Publications

Von Hoff, D.D.; Casper, J.; Bradley, E.; Sandbach, J.; Jones, D.; and Makuch, R.; Association Between Human Tumor Colony-forming Assay Results and Response of an Individual Patient's Tumor to Chemotherapy. American Journal of Medicine, May 1981.

Von Hoff, D.D.; Myers, J.W.; John, J.; Sandbach, J.F.; Pocelindo, R.; Clark, G,; and Coltman, C.A.,;

Phase I Clinical Investigation of 9,10-AnthraCenedicarboxaldehyde BIS (4,5-dihydro-1H-imidazol-2yl) hydrazone dihydrochloride (CL216,942). Cancer Research, Vol. 41, August 1981.

Von Hoff, D.D.; Sandbach, J.F.; Osborne, K.; Metelmann, M.D.; Clark, G.M.; O'Brien, M.D.; and the South Central Human Tumor Cloning Group: Potential and Problems with Growth of Breast Cancer in Human Tumor Cloning System. Breast Cancer Research and Treatment I, 1981.

Sandbach, J., et al.: Direct Cloning of Human Breast Cancer in Soft Agar. Cancer, October 1983.

Von Hoff, D.D.; Clark, G.M.; Stogdill, B.J.; Sarosdy, M.F.; Sandbach, J.F.; and the South Central Texas Cloning Group: A Prospective Trial of a Human Tumor Cloning System. Cancer Research Vol 43: 1926-1931, 1983.

Myers, J.W.; Von Hoff, D.D.; Kuhn, J.G.; Osborne, C.K.; Sandbach, J.F.; Pocelinko, R.: Anaphylactoid Reactions Associated with Bisanthrane Infusions. Investigational New Drugs, 1983.

Osborne, C.K.; Von Hoff, D.D.; Cowan, J.D.: Sandbach, J.F.: Bisanthrane, An Active Drug in Breast Cancer Selected by Screening in the Cloning Assay. Cancer Treatment Reports, Vol 68:2, February 1984.

Mahoney, D.; Steuben, P.; Sandbach, J.; and Fernbach, D.: Extraneural Metastases from Medulloblastoma: Long-Term Survival After Sequentially Scheduled Chemotherapy and Radiotherapy. Medical and Pediatric Oncology, Vol. 14:329-331, 1986.

Von Hoff, D.D.; Sandbach, J.F.; Clark, G.M.; Turner, J.; Forseth, B.F.; Piccart, M.J.; Colombo, N.; Muggia, F.M.: Selection of Cancer Chemotherapy for a Patient by an In Vitro Assay Versus a Clinician. Journal of the National Cancer Institute, Vol. 82, No. 2, January 1990.

Perez, E.A.; Hesketh, P.; Sandbach, J.; et al: Comparison of Single-Cell Oral Granisetron vs. Intravenous Ondonsetron in the Prevention of Nausea and Vomiting Induced by Moderately Emetogenic Chemotherapy: A Multi-Center Double-Blinded Randomized Parallel Study, American Society of Oncology, 1997 (submitted for publication).

Rothenberg, M.; Cox, J.; DeVore, R.; Sandbach, J.; et al: A Multicenter, Phase II Trial of Weekly Irinotecan (CPT-11) in Patients with Previously Treated Colorectal Cancer, Journal of Clinical Oncology, 2001.

Hughesdon, M., and Sandbach, J.; Nurse Oncologist Utilization in a Hematology/Oncology Clinic. American Col. Phys. – Soc. Of Air Force Phys., Williamsburg, Virginia, 1977.

Sandbach, J.; Steinfeld, A.; Schwamm, H.; and Bernard, D.: A formerly Unreported Presentation of Hodgkin's Disease. Amer. Col. Phys. – Society of Air Force Physicians, Williamsburg, Virginia 1977.

Sandbach, J., et al: Assay for Clonogenic Cells in Human Breast Cancer. American Association Clinical Research, San Diego, California, 1980 (Abstract 557).

Sandbach, J.F.; O'Brien, M.D.; Cruz, A.; Clark, G.; Von Hoff, D.D.; and The South Texas Human Tumor Cloning Group. Directed Cloning of Human Breast

Cancer in Soft Agar. American Society of Clinical Oncology, 1981 (Abstract C-71).

Von Hoff, D.D.; Sandbach, J.F.; Osborne, D.K.; Metelman, C.; Clark, G.M.: Growth of Human Breast Cancer in a Human Tumor Cloning System. NCI-EORTA Meeting, Brussels, Belgium, October 1981.

Von Hoff, D.D.; Myers, J.W.; Kuhn, J.; Osborne, C.K.; Sandbach, J.F.; Coltman, C.A.: Phase I and II Trials with Bisanthrane Hydrochloride (BIS). NCI-EORTA Meeting, Brussels, Belgium, October 1981.

Von Hoff, D.D.; Clark, G.A.; Sarosdy, M.; Stogdill, B.; Sandbach, J.F.: Clinical Correlations for a Human Tumor Cloning System. NCI-EORTA Meeting, Brussels, Belgium, October 1981.

Myers, J.W.; Von Hoff, D.D.; Kuhn, J.; Sandbach, J.F.; Pocelinko, R.; Clark, G.; Coltman, C.; and Rodriguez, V.: Phase I Investigation of CL216942 on a Single Dose Intermittent Schedule. American Association of Cancer Research, 1981 (Abstract 689).

Osborne, C.K.; Von Hoff, D.D.; and Sandbach, J.F.: Activity of Bisanthrane in a Phase II Study in Advanced Breast Cancer. ASCO Proceedings, 1982 (Abstract C-336).

Osborne, K.D.; Von Hoff, D.D.; Clark, G.M.; Sandbach, J.F.; O'Brien, M.; and The South Central Texas Human Tumor Cloning Group: The Clonogenic Assay Identified Antagonism in Combination Chemotherapy of Breast Cancer. American Association of Clinical Research, April, 1982 (Abstract 729).

Sandbach, J.F.; Osborne, K.; Von Hoff, D.; Cohen, S.; Gorden, D.; Mims, C.; Ellis, B.; Oines, D.; Whitecon, J.; and Cowan, J.: Bisanthrane, an Active Drug in Breast Cancer Selected by Screening in the Cloning Assay, The 5th Annual Breast Cancer Symposium, 1982 (Abstract 63).

Cowan, J.D.; Sandbach, J.F.; Von Hoff, D.D.; and Clark, G.M.: The Comparative Antitumor Activity of Adriamycin, Mitoxanthrane and Bisanthrane in Human Breast Cancers as Measured by the Cloning Assay, The 5th Annual Breast Cancer Symposium, 1982 (Abstract 38).

Kampe, C.E.; Rodgers, G.P.; Oswalt, J.D.; and Sandbach, J.F.: Exercise-induced Fragmentation Hemolysis: A Simple in Vivo Test to Evaluate Heart Valve Hemolysis, The Southern Medical Journal, 1998 (in press).

Weissman, C.; Sandbach, J.F.; Brooker, R., Ilegbodu, D.; Bell, S.; Asmar, L.: Phase II Study of Weekly Concomitant Taxotere/Carboplatin in Stage IIIB, With Effusion or Stage IV Non Small Cell Lung Cancer Patients Who are < or = Age 65 and Performance Status 2. U.S. Oncology, Houston, Texas. USA.

David Loesch, M.D.; F. Anthony Greco, M.D., Joyce O'Shaughnessy, M.D.; Nicholas Robert, M.D.; Neil N. Senzer, M.D.; Howard A. Burris, M.D.; John D. Hainsworth, M.D.; Sasha Vukelja, M.D.; John Sandbach, M.D.; Frankie Holmes, M.D.; Scot Sedlacek, M.D.; Deborah Lindquist, M.D.; Kristi A. Boehm, M.D.; Feng Zhan, Ph.D.; Lina Asmar, Ph.D.A randomized, multicenter phase III trial comparing regimens of doxorubicin + cyclophosphamide followed by paclitaxel or doxorubicin + paclitaxel followed by weekly paclitaxel as adjuvant therapy for patients with high risk breast cancer.

Thomas Cartwright, M.D.; John Cox, M.D.; Marcus Neubauer, M.D.; Andrew D. McCollum, M.D.; John Sandbach, M.D.; Michael A. Monticelli, M.D.; Kristi A. Boehm, M.S.; Des Ilegbodu, DrPh; Lina Asmar, Ph.D. A Phase II study of gemcitabine plus zoledronic acid in Stage IV cancer of the pancreas.

David Loesch, MD[1,2]; F. Anthony Greco, MD[3]; Joyce O'Shaughnessy, MD[1,4]; Nicholas Robert, MD[1,5]; Neil N. Senzer, MD[1,4]; John D. Hainsworth, MD[3]; Sasha Vukelja, MD[1,6]; John Sandbach, MD[1,7]; Frankie Holmes, MD[1,8]; Scot Sedlacek, MD[1,9]; Deborah Lindquist, MD[1,2]; Jario Olivares, MD[1,11]; Kristi A. Boehm, MS[1]; Feng Zhan, PhD[1]; Lina Asmar, PhD[1] A randomized, multicenter phase III trial comparing regimens of doxorubicin + cyclophosphamide followed by paclitaxel or doxorubicin + paclitaxel followed by weekly paclitaxel as adjuvant therapy for patients with high risk breast cancer ASC Journal of Clinical Oncology, Volume 25, No 18S, June 20, 2007.

Frankie Ann Holmes[1,2]; David Loesch[1,3], Sasha Vukelja[1,4], Joanne L Blum[1,5], Kristi J McIntyre[1], John E Pippen[1,5], John Sandbach[1,6], WJ Hyman, Don A Richards, Kristi Boehm[1], Lina Asmar[1], Joyce O'Shaughnessy[1,5]. Are granulocyte colony-stimulating growth factors (CSF's) needed to prevent febrile neutropenia (FN) for course #1 of adjuvant chemotherapy with "standard" doxorubicin-cyclophosphamide (ASC) Results from two consecutive US Oncology community adjuvant trials.

Stephen E Jones, Michael A. Savin, Frankie Ann Holmes, Joyce A. O'Shaughnessy, Joanne L. Blum,

Svetislava Vukelja, Kristi J. McIntyre, John E. Pippen, James H. Bordelon, Robert Kirby, John Sandbach, William J. Hyman, Pankaj Khandelwal, Angel G. Negron, Donald A. Richards, Stephen P. Anthony, Robert G. Mennel, Kristi A. Boehm, Walter G. Meyer, Lina Asmar. Phase III Trial Comparing Doxorubicin Plus Cyclophosphamide With Docetaxel Plus Cyclophosphamide As Adjuvant Therapy for Operable Breast Cancer. Journal of Clinical Oncology, Vol 24, No 34, December 1, 2006. (DOI: 10.1200/JCO.2006.06.5391)

Eisenbraun A, Wenstrup R, Fry C, Reid, J, Hellerstedt, B, Sailer, L and Sandbach J Hereditary Breast and Ovarian Cancer Testing Integration and Outcomes within Community Oncology Practices. Submitted

[Declaration of Joseph Straus, filed December 23, 2009] [Caption Omitted In Printing] [Exhibits A-I Omitted]

I, Joseph Straus, hereby declare that:

1. I am currently at the Max-Planck-Institute for Intellectual Property, Competition and Tax Law, Munich, as a Director Emeritus.

2. I studied law at the University of Ljubljana, Slovenia, receiving a law-diploma in 1962. I continued my studies at the University of Munich, Germany, receiving first a certificate in German private and public law in 1963 and a doctorate of juridical science in 1968. In 1986, I attained habilitation at the University of Ljubljana. I was awarded the honorary grades of a Doctor Honoris Causa by the University of Ljubljana in 2001 and by the University of Kragujevac, Serbia, in 2003.

3. From 1968 until 1977, but partly already before, I was in private practice. Since 1977, I have practiced at the Max-Planck-Institute for Foreign and International Patent, Copyright and Competition Law in Munich, which was renamed in 2002 as the Max-Planck-Institute for Intellectual Property, Competition and Tax Law. At that Institute, I was first the Head of the Department primarily responsible for patents and I have been a Director there since 2001 until my retirement as of end of 2008.

4. Between 2001 and 2004, I was the Managing Director of the Institute. Until the end of 2008, I was also the Chair of the Managing Board of the Munich Intellectual Property Law Center ("MIPLC"), which I

co-founded in 2003. My main area of interest is patent law, and in particular, the field of chemical and biotech inventions.

5. The academic positions that I currently hold include Nominated Full Professor for Intellectual Property Law, University of Ljubljana (since 1986); Professor of Law, University of Munich, where I have taught patent law since 1990; and Marshall B. Coyne Visiting Professor of International and Comparative Law, George Washington University School of Law, Washington D.C., where I teach a course on chemical and biotechnology related patents. Additionally, I am a Visiting Fellow at the Hoover Institution, Stanford University. I am also an Honorary Professor of several universities including Tongji University, Shanghai and Huazhong University for Science and Technology, Wuhan, China.

6. During my career, I have held a number of other academic positions and have been a Visiting Professor at several establishments including Cornell Law School, Ithaca, New York (1989-1998); Toronto University (Spring 2005), Renmin University, Beijing (Spring 2005); and George Washington University, Washington D.C. (2001-2004).

7. I act or have acted as consultant to over ten international organizations and national state authorities including the Organization for Economic Cooperation and Development ("OECD"), World Intellectual Property Organization ("WIPO"), the World Bank, the United Nations Industrial Development Organization, the European Commission, the European Patent Office, the Swiss Intellectual Property Institute, the German Government as well as the Swiss Government and

the German Parliament. As an expert on the protection of biotechnological inventions, I have testified before the Committee on Legal Affairs and Citizen's Rights of the European Parliament, before the Committee on Legal Affairs of the German Parliament (Bundestag), and before a Special Committee of the Austrian Parliament.

8. Over my career, I have held positions in several committees or advisory bodies of international governmental as well as non-governmental organizations, including the Advisory Board of the WIPO Worldwide Academy; the Standing Advisory Committee before the European Patent Organization ("SACEPO"); the Advisory Board of the Research Fund of the European Patent Office; the Programme Committee of the International Association for the Protection of Industrial Property (Chair, 1997-2006); the Intellectual Property Rights Committee of the Human Genome Organization (Chair 1995-2006); and the International Association for the Advancement of Teaching and Research in Intellectual Property (President, 1993-1995). At present, I am the Vice-president of the German Association for the Protection of Industrial Property and Copyright ("GRUR") and Chair of the Law Section of the Academia Europaea.

9. In 1999, I was elected Katz-Kiley Fellow of the Houston Law Center, Houston. In 2000, I was awarded the "Science Award 2000" of the Foundation for the German Science (Stifterverband für die Deutsche Wissenschaft) as the first non-scientist. In 2005, I was awarded the "Commander's Cross" of the Order of Merit of the Federal Republic of Germany

(Großes Verdienstkreuz des Verdienstordens der Bundesrpublik Deutschland). From 2003-2006, I was selected as one of the 50 most influential people in intellectual property by the Journal "Managing Intellectual Property" and was made a Member of Honour of the International Association for the Protection of Industrial Property ("AIPPI") in 2006. I was inducted into the Intellectual Asset Management Magazine IP Hall of Fame in 2007. In that same year, I was also given the Venice Award for Intellectual Property for commitment to the promotion of intellectual property culture.

10. I am the author or co-author of some 300 publications in the field of intellectual property. A full list of my publications is provided in **Ex.** A. Details of the various advisory and academic positions I have held during my career is set out in the bibliography which is provided at **Ex.** A.

11. In the past, I have provided expert opinions in connection with various patent disputes in Germany, Europe, the United States of America, Japan and Brazil for a great number of companies, including U.S., Europe and Japan based companies.

12. At present, I am acting as Consultant to a number of companies, however, entirely unrelated to the case at hand and to the parties involved.

13. In view of the subject matter at hand, I may in particular emphasize the following:

14. In 1985, I co-authored (with Prof. F.K. Beier und St.R. Crespi) a study published by OECD, entitled "Biotechnology and Patent Protection – An International Review," which was translated into French, German and Japanese language and which

presented the very first study in the area of patenting biotechnological inventions at an international level. Also, in 1985, I prepared a study for WIPO entitled "Industrial Property Protection of Biotechnological Inventions. Analysis of Certain Basic Issues," (WIPO Document BIG/281), which was translated into French, German and Spanish language and which served as the basis for deliberations of a Special Committee of WIPO on the Protection of Biotechnological Inventions.

15. Between 1986 and 1988, I served as consultant to the European Commission in the preparation of the first draft for a Directive on the legal protection of biotechnological inventions. I was the sole drafter of the Explanatory Memorandum to that document. Later on, I assisted the EC Commission in the deliberations with the EU Council and testified before the Committee on Legal Affairs and Citizen's Rights of the European Parliament in the last hearing before adoption of the European Directive 98/44/EC (the "EU Directive"); **Ex.** B.

16. From 1995 to 2006, I was the Chair of the Intellectual Property Rights Committee of the Human Genome Organization ("HUGO"), whose members at that time were *inter alia* Professors Rebecca Eisenberg (Michigan State University), Eric Lander (MIT), Sir John Sulston (Cambridge), David Cox (Stanford). In this capacity, I was co-responsible for a number of statements on issues of patentability of human DNA sequences, which were adopted and published by HUGO's Council.

17. It should be noted that in 1997, when I was acting as Chairman of HUGO's IPR Committee, we issued a statement on patenting issues related to the

early release of raw sequence data ("HUGO 1997 Statement"). *See* **Ex.** C. This statement embodied the principles we adopted in the organization, and particularly set out to inform the scientific and legal community that HUGO did *not* oppose the "patenting of useful benefits derived from genetic information." **Ex.** C. Quite the contrary, HUGO was in favor of patenting isolated DNAs with a known function. What HUGO opposed was patents on express sequence tags ("EST")[1] which had no known function or utility. The United States adopted this standard, which has been the state of the law since *Fisher*. *See In re Fisher*, 421 F.3d 1365 (Fed. Cir. 2005) (affirming the USPTO's refusal to grant a patent on ESTs with unknown function or utility). I note that, Sir Sulston, Plaintiffs' declarant, contrary to the positions he has taken in this case (*See*, *e.g.*, Sulston Decl. ¶¶ 37-38.), was indeed not only a member of HUGO at this time, but also a signatory of the 1997 HUGO Statement.

18. Between 2004 and 2006, I chaired an OECD Expert Group which in 2006 successfully developed detailed principles and best practices for the licensing of genetic inventions in order to ensure that therapeutics, diagnostics and other products and services employing genetic inventions are made readily available on a reasonable basis.

19. I have reviewed the following documents: Plaintiffs' Memorandum of Law in Support of Motion for Summary Judgment; Plaintiffs' Rule 56.1

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[1] An EST (Expressed Sequence Tag) is a short sequence of the complementary DNA that was expressed by the full-length gene.

Statement of Material Facts; Declaration of Sir John E. Sulston, Ph.D. of August 17, 2009; Declaration of Myles W. Jackson of August 18, 2009; and United States Patent Nos. 5,747,282 ("the '282 patent"); 5,837,492 ("the '492 patent"); 5,693,473 ("the '474 patent"); 5,710,001 ("the '001 patent"); 5,753,441 ("the '441 patent"); 6,033,857 ("the '857 patent"), (collectively "Myriad patents"); *Utility Examination Guidelines*, 66 Fed. Reg. 1092 (January 5, 2001), **Ex.** D ("2001 Guidelines"); Decision of June 6, 2007 of the Opposition Division in connection with the EP 0 705 903 patent (granted May 23, 2001), **Ex.** E; Board of Appeal Decision T 0666/05 of November 13, 2008 in connection with the EP 0 705 903 patent, **Ex.** F; Board of Appeal Decision T 1213/05 of September 27, 2007 in connection with the EP 0 705 902 (granted November 28, 2001), **Ex.** G; Straus *et al.*, "Genetic Inventions and Patent Law – An Empirical Survey of Selected German R & D Institutions," Published by Max Planck Institute for Intellectual Property, Competition and Tax Law, Munich 2004, **Ex.** H; Walsh *et al.*, 2005, *Science*, "View from the Bench: Patents and Material Transfers," 309:2002-03, **Ex.** I ("Walsh 2005").

I. ISOLATED NUCLEIC ACID PATENTS – A EUROPEAN PERSPECTIVE

A. SCIENTIFIC BACKGROUND

20. Genes are to be understood as fundamental physical and functional units of heredity. Genes are located in a particular position on a particular chromosome. Genes encode specific functional products, such as a protein or RNA molecule. Genes are of double nature: On the one hand, they are

chemical substances or molecules. On the other hand, they are physical carriers of information, *i.e.*, where the actual biological function of this information is coding for proteins. Thus, inherently genes are multifunctional.

21. Since the completion of the raw sequence of the human genome not only do we know that we only have some 20,000–25,000 genes, but also that some 40 per cent of the gene products are alternatively spliced. Therefore, genes encode for more than one protein, depending on the combination of exons read in an open reading frame, or even depending on the direction in which the exons are read. Thus, many genes are rendered multifunctional based on this splicing mechanism. Moreover, DNA molecules as physical carriers and information are multifunctional under another important aspect: they hybridize to other DNA molecules, a property I would like to describe as an actually non-biological function. Thus, by virtue of this property, DNA molecules can be used, for instance, as DNA probes, and diagnostic markers.

B. WHAT CONSTITUTES AN INVENTION IN THE CASE OF ISOLATED NUCLEIC ACID PATENTS – A COMPARATIVE ANALYSIS WITH OTHER PRODUCT INVENTIONS

22. Generally, product inventions relate to: synthetic molecules produced in a lab; chemical substances isolated from natural environment; and DNA molecules of human origin, respectively. I will discuss whether essential differences exist between these different forms of chemical compounds, and

secondly, if there are such differences, whether they require different legal treatment.

1. Synthetic Molecules

23. Synthetically produced new chemical substances are molecules of an arbitrary formula. They are new in an absolute sense and are in principle without an actual biological function. Such molecules are producible in arbitrary – unlimited variations. Finding a first surprising property, for instance a therapeutic effect, of such new, *i.e.*, not pre-existing molecule, even if routinely produced or detected, justifies patent protection. In other words, the essence of the invention is in "making the absolutely new substance available" to the public. The substance made available, in combination with the disclosure of the surprising therapeutic effect, opens up an entire new field for further research. Third parties can search for, for instance, further therapeutic uses, or they can experiment with the disclosed new formula, for instance, by adding, exchanging or deleting protection groups, in order to achieve other useful effects. To my understanding, in such circumstances "absolute" protection is justified and in line with the spirit and purpose of patent law. Without the new molecule and its "invented" property, others could not embark on further research.

2. Chemical Substances Isolated from the Natural Environment

24. In case of chemical substances isolated from the natural environment, the assessment is similar, although such substances are "new" only in the sense

of not being previously available to the public. For example, Lovastatin, a cholesterol-lowering agent was isolated from *Monascus rubber* and various species of *Aspergilus terreus*, a microorganism. In such microorganisms, Lovastin's function by no means is lowering cholesterol. Thus, Lovastatin, and many other natural products, in their natural environment, in principle, typically have no actual biological function or use. Alternatively, the function of the chemical substance as "isolated" is distinct from that as it exists in nature. Moreover, such substances are available in unlimited numbers in nature. Thus, a finding of a first surprising property, such as lowering the blood cholesterol level in the case of Lovastatin, justifies for the very same reason the same treatment as in the case of synthetically produced new chemical molecules. Once the formula of Lovastatin was disclosed, the research in the entire area of the class of statins was opened up and eventually ended in inventing a great number of other new cholesterol-lowering agents.

3. DNA Molecules

25. As indicated above, human genes are biochemical substances as well as physical carriers of information. They have one or more related or unrelated actual, pre-determined biological function(s). They code for various proteins, for instance receptors, structural or regulatory proteins, etc. They are available – producible – only in limited numbers. The actual goal of research in this area is aimed at identifying and deciphering their actual nucleotide sequences, *i.e.*, the exact location and sequence of the gene, in order to find and exploit its actual and pre-determined biological function(s). This

information can be used to make primers and probes for use in diagnostics.

26. Once the actual nucleotide sequences, *i.e.*, the exact location and sequence of the gene, is identified and deciphered, the focus of the invention should be shifted from the "making available" of the DNA, to finding the surprising property(ies), function(s). The identification of a specific open reading frame of a gene will involve "inventive" activity. Thus, "making available of the sequence" is playing the same role as in the case of synthetic molecules and chemical substances isolated from their natural environment. Isolation of such DNA molecules can thus constitute an invention fulfilling all the patentability requirements and deserving "absolute" protection.

II. A UNIFORM WORLD-WIDE APPROACH TO PATENTING ISOLATED NUCLEIC ACIDS

27. Although the appropriateness of granting patents on isolated DNA and other isolated nucleic acids continues to be publicly debated, the position of the official patent authorities in OECD has been clear and consistent for some time. From the standpoint of patent offices in Europe, especially the European Patent Office ("EPO"), genetic material is not seen as a special case requiring treatment different from chemical compounds and other products. This view is shared by the patent offices of the United States and Japan. Common ground between the EPO, the United States Patent and Trademark Office ("USPTO") and the Japanese Patent Office ("JPO") has already been reached with respect to patents on isolated nucleic acids.

28. Mere determination of a DNA sequence is not enough for patentability. But, where the inventor is the first to identify a gene and its useful function, to isolate and clone the nucleic acid of the gene and thereby make synthetic copies of the nucleic acid that are available for use in diagnosis or therapy, patent offices world-wide accept that this is the kind of invention for which a patent can be granted.

III. THE EUROPEAN APPROACH

29. Patenting of biotechnology inventions, including patenting DNA molecules corresponding to genes, has been contentious and involved, at times, heated public debate. All of such discussions influenced the debate concerning the implementation of the EU Directive of the European Parliament and the Council on the legal protections of biotechnological inventions. The EU Directive 98/44/EC was adopted in July 1998 after a tense and controversial debate.

30. According to the EU Directive, assuming that a DNA sequence is novel, *i.e.*, not previously publicly known or used, and that other criteria for patentability are met (*i.e.*, industrial applicability utility, non-obviousness, sufficient disclosure), the isolated substance of the DNA itself is patentable. To be precise, the claims concern not the sequence as abstract information, but a molecule which has a defined chemical structure (as nucleotide sequence) and function. This type of product claim will often be qualified in some respect, *e.g.*, by the limitation of "isolated" or "purified," especially if the substance exists in nature.

31. Specifically, the approach adopted by the EU Directive is that a nucleic acid corresponding to a

complete or part of a gene, even if its structure is identical to that of a natural element, may constitute a patentable invention, if isolated from the human body or otherwise technically produced. **Ex.** B at Article 5(2). Indeed, the natural pre-existence of biological material alone does not constitute a patentability obstacle. **Ex.** B at Article 3(2). The EU Directive established that no patent can cover a substance *in situ* in the human body. Rather, the patent must cover the isolated substance. It is my understanding that the United States Patent and Trademark Office has a similar policy, in that it requires product claims to genetic materials be limited to the purified and isolated material. 2001 Guidelines; **Ex.** D.

32. Apart from the above restriction, an isolated DNA can be claimed as the substance *per se*, without limitation to any particular process of purification or isolation and without any limitation as to its intended use. In patent parlance, this is known as a "product per se" claim and it confers "absolute product protection." Granting "product per se" patents for genetic inventions is consistent with the established practice for new pharmaceuticals and other chemical compounds. The trend in many countries over the years has been to allow such product claims, as against previous more restrictive policies of allowing claims only to the particular chemical processes described in the patent application for making end products. In fact, the World Trade Organization ("WTO") Trade Related Intellectual Property Rights ("TRIPS") Agreement requires patent protection to be available for process and product claims in all branches of technology,

without discrimination. TRIPS Agreement at Article 27 (1)).

33. Under the EU Directive, the disclosure of a mere DNA sequence without indication of a function does not contain any technical information and is therefore not a patentable invention (EU Directive at Recital 23), even if the method of manufacture is indicated. On the other hand, the industrial applicability of the isolated DNA, in other words its function, has to be specifically disclosed in the patent application as filed. EU Directive at Recital 22, last sentence, Article 5(3). Where the use of a sequence or partial sequence of a gene for making a protein is claimed, the protein or part protein and its function have to be specified. EU Directive at Recital 24. If therapeutic or diagnostic uses are claimed, the disorder to be diagnosed or treated must be specifically indicated. Thus, the European legislator has made the function of a claimed DNA molecule an integral part of the notion of an invention (inventive concept) of a chemical compound invention, at least in this area.

34. Under the EU Directive, protection of a product, which consists of or contains genetic information, *i.e.*, a gene sequence, extends to any product – except man – in which this product is incorporated and in which the genetic information is contained and performs its function. **Ex. B** at Article 9.

IV. MYRIAD'S COMPOSITION OF MATTER CLAIMS COMPLY WITH THE EP PATENT LAWS

35. I reviewed claims 1, 2, 5, 6, and 7 of the '282 patent; claim 1 of the '473 patent; claims 1, 6, and 7 of the '492 patent. These claims all relate to isolated DNA molecules comprising either the *BRCA*1 or *BRCA*2 DNA. For ease of reference, I will refer to such claims as the "isolated DNA" claims.

36. Under the EU Directive, the Implementing Regulations to the European Patent Convention ("EPC") and case law interpretation of it, "isolated and purified" DNA molecules are patent-eligible subject matter. Thus, Myriad's isolated DNA claims are patent-eligible. The European Patent Office ("EPO") and Supreme Courts of the EU Member States, to my knowledge, have never challenged the validity of patents granted by the EPO Boards of Appeal for "isolated and purified" DNA based on the grounds of their eligibility for patent protection.

37. As I mentioned above, I reviewed the decision of June 6, 2007 of the Opposition Division in connection with the EP 0 705 903 patent; Board of Appeal Decision T 0666/05 of November 13, 2008, confirming the holding of the Opposition Division and maintaining the EP 0 705 903 patent, and the Board of Appeal Decision T 1213/05 of September 27, 2007, maintaining the EP 0 705 902 patent. **Exs.** E-G. It should be noted that all the arguments that Plaintiffs have raised in this case (*see* Plaintiffs' Statement of Material Facts) were also raised during the Opposition Proceedings of these counterpart EP patents. In each case, these arguments were rejected by the Boards of Appeal.

38. Indeed, as reiterated by the Board of Appeal, an independent judiciary body, there simply is no bar to the patenting of isolated human DNA. Like plaintiffs in the U.S. case, the opponents in Europe attempted to raise socio-economic consequences of patenting of the claimed subject matter as a basis for denying patentability of Myriad's invention. But, like the Courts in the United States, those in Europe have all repeatedly ruled that isolated nucleic acids such as those claimed in the Myriad patents constitute patent-eligible subject matter. Any change in the law is not within the province of the EPO or the national courts of the states parties to the European Patent Convention ("EPC") – neither is it within the province of the U.S. courts. Anyone challenging the Myriad patents would need to access another vehicle – perhaps, the Legislature.

V. EFFECT OF ISOLATED NUCLEIC ACID PATENTS ON BASIC RESEARCH, MEDICAL AND CLINICAL RESEARCH, INNOVATION AND COMMERCIALIZATION

39. While many have criticized the impact of genetic invention patents on access to the information and technologies covered by DNA patents, the available evidence does not suggest a systematic breakdown in the research and development of genetic inventions, once a particular isolated nucleic acid corresponding to a gene is patented. To the extent there are any concerns regarding the potential for over-fragmentation of patent rights, blocking patents, or abusive monopoly positions, they appear anecdotal and not supported by any actual studies. Below, I summarize the result

of two such empirical studies that negate the misconception that biotechnology patents have slowed biomedical research.

A. An Empirical Study in Germany

40. In 2002, the German government commissioned a study on "Genetic Inventions and Patent Law," which I conducted while at the Max Planck Institute for Foreign and International Patent, Copyright and Competition Law. **Ex.** H. The purpose of the German survey was to gain information from an objective viewpoint concentrating on the challenges of potential patentees for patenting genetic inventions and to provide evidence about the licensing practices relating to genetic inventions. Furthermore, the German survey was aimed at elucidating whether specific problems arise from the application of patent law on genetic inventions, in particular from patents on isolated DNA. As I indicated in a presentation, which I offered on the Survey in a January 2002 workshop, entitled "Genetic Inventions, Intellectual Property Rights and Licensing Practices," jointly organized by the OECD and the German Federal Ministry for Education and Research in Berlin, the overall goal of the survey was to verify concerns expressed on negative impact of patents in genomics as set forth in the EU Directive 98/44. Interviews were carried out at 25 institutions, including large pharmaceutical companies, biotech start-ups, clinical institutions associated with universities and other publicly funded research institutes and clinical institutions involved in genetic testing.

41. The survey specifically investigated, *inter alia*, whether there was reluctance to enter particular

research fields in which gene related patents have been granted. No such tendency was observed. Interestingly, the great majority of those interviewed across the entire surveyed group clearly favored the so-called absolute product patent protection of isolated nucleic acids. Those surveyed opposed any discrimination of this area of research and development as compared with the protection which classical chemical inventions enjoy. Of all the groups surveyed, including clinical institutions associated with universities, no specific problems of licensing were reported. Only some of those interviewed indicated a reduced interest for research in further uses of inventions patented for third parties.

42. Indeed, my study showed that all institutions surveyed were able to cope with the patent system ***as is*** in a satisfactory manner. We could not detect any support for a special regime for protecting genetic inventions. It should also be added that for those interviewed, there is a possibility for applying for a compulsory license, available under Section 24 German Patent Act ("GPA") which allows the grant of such a license, if such a license would be in public interest. Alternatively, in cases of a dependent patent claiming an invention, which involves an important technical advance of considerable economic significance in relation to the invention covered by the dominant patent, so-called dependency compulsory license would be available under the GPA. To my knowledge, neither in Germany nor in any other EU Member State a compulsory license has ever been applied for any of Myriad patents.

43. Finally, my study also found that patents on research tools, including isolated DNA molecules, have not had a discernible effect on the cost or pace of research in Germany, and the survey results suggested several reasons for this. First, some research tools are staple goods, like enzymes, which can be purchased without declaring their intended use. Second, it is difficult to detect infringement of research tools which are used behind laboratory doors. While end products may be suspected of having been developed using a patented research tool, many biotechnology companies do not yet have such commercialized products, making it difficult to claim infringement. Third, public research bodies claim that their staff are often unaware of the legal implications of using patented research tools. In short, many groups act as if an "informal research exemption" exists for the use of patented research tools.

B. An Empirical Study in the United States

44. In May 2006, I attended a Conference Organized by the OECD among other organizations entitled "Research Use of Patented Inventions," where I was also a presenter. This conference was organized, in part, to address the concerns in the scientific and legal communities in accessing biotechnology inventions that are protected through the patent system. One presenter of note at this conference was John P. Walsh, associate Professor of Sociology at the University of Illinois, Chicago. *CSIC/OECD/OEPM Conference*, Madrid, Spain, May 18-19, 2006; John P. Walsh, "Roadblocks to Accessing Biomedical Research."

45. Walsh's study consisted of interviews with executives and researchers at biotechnology and pharmaceutical firms and research personnel and administrators at several universities. The objective of the study was to evaluate whether the "tragedy of the anti-commons"[2] is indeed a reality in biomedicine and whether patent rights to certain research tools are retarding innovation. Specifically, Walsh examined the impact of patents and licensing on access to knowledge and material inputs for academic biomedical research; the limitations on subsequent discovery and improvements imposed by assertion of patent on upstream foundational discoveries, such as discovery of genes; and the effect patents on research productivity.

46. Walsh reported the results from a survey of 1125 academic researchers (including university, nonprofits and government labs), which yielded 414 responses (adjusted response rate of 40%).

47. Walsh's results showed that there was little evidence so far of breakdowns in negotiations over patent rights or evidence that biomedical research has slowed as a result of biotechnology patents, including gene patents. Indeed, firms and research organizations in the United States reported "working solutions" which allow them to continue to innovate relatively unimpeded. Solutions included license negotiations where necessary or the avoidance of patent obstacles by working around the claims.

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[2] The "tragedy of the anti-commons," a term coined by Heller and Eisenberg (1998), refers to a situation where there are numerous property right claims over the building blocks necessary for research and development.

Firms also chose to ignore or infringe patents, to challenge patents and litigate, to move offshore or to put innovations in the public domain. Thus, it would appear that access to patented technology has rarely, if ever, been blocked.

48. Further, in a 2005 article published in the journal *Science*, John P. Walsh and colleagues report the findings from a survey conducted on 414 biomedical researchers in universities, government, and nonprofit institutions to determine the effect of patents on biomedical research and material transfers. **Ex.** I at 2002. The researchers found that "few academic bench scientists currently pay much attention to the others' patents." *Id.* Moreover, of the "32 respondents who were aware of relevant IP, four reported changing their research approach and five delayed completion of an experiment by more than one month. No one reported abandoning a line of research. Thus, of 381 academic scientists . . . none were stopped by the existence of patents, and even modifications or delays were rare." *Id.*

49. I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and believe.

/s/ Joseph Straus

Executed on: December 22, 2009

Joseph Straus

EXHIBITS A-I

[EXHIBITS A-I OMITTED]

[Declaration of Nancy Linck, filed December 23, 2009] [Caption Omitted In Printing] [Exhibits 1-3 Omitted]

I, Nancy J. Linck, hereby declare that:

1. I am currently a member of Rothwell, Figg, Ernst & Manbeck, P.C., 1425 K Street, NW, Suite 800 Washington, DC 20005.

2. I specialize in intellectual property law, particularly in the biotechnology and pharmaceutical areas. I have experience in private and corporate practice, including consulting and litigation at both trial and appellate levels and inter partes matters before the U.S. Patent and Trademark Office ("USPTO"). From 1997 to the present, I have served as an adjunct professor at George Washington University and Georgetown Law Center, lecturing on current issues in intellectual property law. I have published numerous articles in the intellectual property area; these are listed in my *curriculum vitae*, attached as Exhibit 1.

3. I served as an Administrative Patent Judge on the USPTO's Board of Patent Appeals & Interferences in the Board's biotechnology practice group from May 2006 to February 2008. In this capacity, I was responsible for hearing and deciding appeals from Examiners' rejections in the pharmaceutical and biotechnology sectors.

4. Before becoming an Administrative Patent Judge, I was Deputy General Counsel, IP & Trade for the Biotechnology Industry Organization ("BIO") where I was responsible for all intellectual property and trade secret related issues.

5. During the 2002-2005 period, I was Senior Vice President, Intellectual Property and Regulatory Affairs, and Chief Compliance Officer for Guilford Pharmaceuticals ("Guilford"). I was a member of the executive management team at Guilford and was responsible for all aspects of intellectual property, both domestically and internationally. While at Guilford, I also served as Senior Vice President & General Counsel and was responsible for the company's legal matters and all aspects of intellectual property.

6. I served as the Solicitor of the United States Patent and Trademark Office ("USPTO") from August 1994 until November 1998; at that time, the highest legal position in the USPTO, i.e., the Commissioner's General Counsel. As Solicitor, I represented the USPTO in patent, trademark and administrative law litigation and was heavily involved in all legal matters within the USPTO, including evaluation of proposed changes to relevant statutes, rules, and the Manual of Patent Examining Procedure ("MPEP"). In addition, I was responsible for what ultimately became known as the USPTO's "legal guidelines," and personally played a lead role in their drafting and adoption by the USPTO.

7. With respect to the USPTO's litigation, I oversaw over 100 appeals at the U.S. Court of Appeals for the Federal Circuit ("Federal Circuit") and a number of district court cases. Among these cases were *Wu v. Wang*, *Hoechst-Roussel Pharms v. Lehman*, *Merck & Co. v. Kessler*, *Astra v, Lehman*, *In re Baird*, *In re Morris*, *In re Portola Packaging Inc.*, *In re Recreative Tech. Corp.*, and *State Street Bank v. & Trust Co. v. Signature Fin. Group, Inc.*, 149 F.3d

1368 (Fed. Cir. 1998) (a case in which the Federal Circuit adopted the USPTO's legal guidelines relating to the patent-eligibility of computer-related inventions under § 101). In addition, I assisted the Department of Justice in intellectual property cases before the U.S. Supreme Court, including *Lehman v. Zurko*, *Markman v. Westview Instruments*, and *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*

8. Between 1991 and 1994, I was a partner at the intellectual property law firm, Cushman, Darby & Cushman, Washington, D.C. While at Cushman, Darby & Cushman, I represented a number of clients in prosecution and litigation matters, including *Haworth v. Steelcase*, *Perkins v. Kwon*, and *Bigham v. Godtfredsen*.

9. I received my J.D., magna cum laude, from Western New England College School of Law in 1984. In 1986 and 1987, I was a Federal Circuit law clerk for the Honorable Pauline Newman.

10. Prior to my legal education, I received my Ph.D. and M.S. in Inorganic Chemistry from University of California, San Diego (1982) where I studied transition metal complex reactions (organic molecules with metal centers). In 1973, I received a B.S., with honors, in Chemistry from University of California, Berkeley. I recently received my M.S. in Biotechnology from John Hopkins University (2009). My work toward my M.S. included an in-depth study of nucleic acid molecules (DNA and RNA) and their function and structure.

11. I reviewed the following documents: Plaintiffs' Memorandum of Law in Support of Motion for Summary Judgment; Plaintiffs' Rule 56.1 Statement

of Material Facts; Declaration of Sir John E. Sulston, Ph.D. of August 17, 2009; Declaration of Myles W. Jackson of August 18, 2009; and United States Patent Nos. 5,747,282 ("the '282 patent"); 5,837,492 ("the '492 patent"); 5,693,473 ("the '473 patent"); 5,710,001 ("the '001 patent"); 5,753,441 ("the '441 patent"); and 6,033,857 ("the '857 patent"). (collectively "Myriad patents").

I. THE USPTO ADMINISTERS THE LAWS ENACTED BY CONGRESS

12. The USPTO is an administrative agency charged with examining patent applications and issuing U.S. patents, if the applications meet the statutory requirements of Title 35. The USPTO must apply the laws Congress has enacted, as interpreted by the Federal Circuit and the Supreme Court. The USPTO has no policy-making authority and, in fact, cannot even adopt substantive rules in doing its job. *In re Alappat*, 33 F.3d 1526 (Fed. Cir. 1994); *Tafas v. Kappos*, --- --, 2009 WL 3806451 (Fed. Cir. Nov. 13, 2009).

13. In the 1994 to 1995 time period, Commissioner Bruce Lehman charged me with determining whether the USPTO was following controlling law with respect to issuing patents for biotechnology inventions. As Solicitor, Commissioner Lehman asked me to study the relevant law and determine what it required the USPTO to do in examining biotechnology patent applications. As part of that effort, I reviewed the precedential cases involving patentability under § 101, particularly focusing on Federal Circuit and Supreme Court cases and those relied upon by these two courts.

14. The threshold issue we investigated was whether biotechnology inventions, such as isolated DNA and RNA molecules were eligible for patent protection under § 101. After reviewing and discussing the relevant cases, I and others working with me on the project concluded that the law dictated granting patents on such biotechnology inventions, if they satisfied the other statutory requirements, particularly that of utility under § 112.

15. In fact, we found that rejections under § 101 in cases relating to biotechnology and pharmaceutical technology rarely had been sustained by the federal courts. Generally speaking, in those rare cases, the § 101 rejection was sustained either because the patent applicant had failed to disclose any utility for the invention or the asserted utility was not credible. As a result, we developed and issued the first version of our § 101 guidelines (hereafter "1995 Guidelines") to provide guidance to patent examiners to ensure compliance with the law. Exhibit 2; *Utility Examination Guidelines*, 60 Fed. Reg. 36263 (1995) (reproduced in MPEP § 706.03(a)(1) (July 1998)). In the 1995 Guidelines, we identified the tests set forth by the Supreme Court in *Diamond v. Chakrabarty*, 447 U.S. 303 (1980). The tests are identified in the MPEP § 2105 (July 1998):

(A) "the laws of nature, physical phenomena and abstract ideas" are not patentable subject matter.

(B) A "nonnaturally occurring manufacture or composition of matter – a product of human ingenuity – having a distinctive name, character, [and] use" is patentable subject matter.

(C) '[A] new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise. Einstein could not patent his celebrated $E=mc^2$; nor could Newton have patented the law of gravity. Such discoveries are 'manifestations of ... nature, free to all men and reserved exclusively to none.'"

(D) "[T]he production of articles for use from raw materials prepared by giving to these materials *new forms, qualities, properties, or combinations whether by hand labor or bu machinery"* [emphasis added] is a "manufacture" under 35 U.S.C. 101.

16. In addition to identifying the above *Chakrabarty* tests, our analysis of the relevant case law led us to conclude that the Court (1) did not limit *Chakrabarty* to genetically engineered living organisms and the Court (2) had "enunciated a very broad interpretation of 'manufacture' and 'composition of matter.'" *See id. See also infra* notes 3 & 4 (quoting the Court's interpretation of these terms). I note that both these terms encompass Myriad's product claims (hereafter "DNA claims") under the Court's definitions.

17. Finally, while recognizing the need to determine patent eligibility under § 101 on a "case-by-case basis following the tests set forth in *Chakrabarty*," we determined that the law required the USPTO to find patent eligible any "non-naturally

occurring manufacture or composition of matter." *Id.*

18. An analysis of the precedential cases we considered prior to issuing the 1995 Guidelines was included in the later published *Utility Examination Guidelines*, 66 Fed Reg. 1092 (January 5, 2001) (Exhibit 3) (hereafter the "2001 Guidelines"). My analysis of these cases, along with that of other cases discussed in the 2001 Guidelines, is given below. *See infra* at ¶¶ 29-42; 50-69; & 77.

II. THE UNITED STATES PATENT LAWS

19. We began our legal analysis by acknowledging that our founding fathers recognized the importance of fostering innovation and thus provided Congress with broad powers to "promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive right to their respective writings and Discoveries." U.S. Const, Art. 1, § 8, cl. 8.

20. Pursuant to these broad powers and its policy-making authority, Congress enacted the patent statutes. First enacted in 1790 (Act of April 10, 1790, ch. 7, 1 Stat 109) and found today in Title 35 of the United States Code, these statutes provide patent protection for a limited time period to whomever "invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof . . . , subject to the conditions and requirements of this title." 35 U.S.C. § 101. The "conditions and requirements" referenced in § 101 are found in 35 U.S.C. §§ 102, 103 and 112, *i.e.*, the invention must be novel, not obvious and described in a way that one skilled in the relevant field can make and use it.

21. The use of the expansive term "any" in § 101 reflects Congress' intent not to place restrictions on the subject matter for which a patent may be obtained beyond those specifically recited in § 101. Indeed, the Supreme Court has acknowledged that Congress intended § 101 to extend to "anything under the sun that is made by man." *Chakrabarty*, 447 U.S. at 309 (quoting S.Rep. No. 1979, 82nd Cong., 2nd Sess., 5 (1952); H.R.Rep. No. 1923, 82nd Cong., 2nd Sess., 6 (1952)).

22. We further acknowledged that, despite the apparent sweep of § 101, the Supreme Court has held that three distinct categories of subject matter, namely "laws of nature, natural phenomena, and abstract ideas," are not entitled to patent protection. *Chakrabarty*, 447 U.S. at 309; *see also*, *Diamond v. Diehr*, 450 U.S. 175, 185 (1981).

23. However, there is no basis in law for any other category of subject matter excluded from patent eligibility. Thus, Plaintiffs improperly read in a fourth category of excluded subject matter – isolated products of nature – into the Supreme Court line of cases. Pl. Br. at 19-20. The Supreme Court has never held that isolated products of nature are *per se* not patent eligible.

24. It is improper to read into § 101 limitations as to the subject matter that may be patented where the legislative history does not indicate that Congress clearly intended such limitations. *See Chakrabarty*, 447 U.S. at 308 ("We have also cautioned that courts should not read into the patent laws limitations and conditions which the legislature has not expressed.") (internal citations omitted).

25. As recognized by the Supreme Court, the "authority of Congress is exercised in the hope that '[t]he productive effort thereby fostered will have a positive effect on society through the introduction of new products and processes of manufacture into the economy, and the emanations by way of increased employment and better lives for our citizens.'" *Chakrabarty*, 447 U.S. at 307 (quoting *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 480 (1974)) (other citations omitted).

26. Following the Supreme Court decision in *Chakrabarty*, patent law operated exactly as Congress hoped it would by promoting science in the biotechnology area and thereby creating a new industry, along with increased employment and better lives for all of us by providing new products such as Myriad's diagnostic tools for breast and ovarian cancer, which are covered by the claims of the Myriad patents.

27. The Myriad patents generally relate to the identification of the *BRCA*1 and *BRCA*2 genes, which are associated with breast and ovarian cancer. The widespread adoption of the diagnostic tests protected by the patents suggests the tests represent a significant breakthrough for the development of cancer diagnostics and therapeutics which would not have happened but for the patent system in effect. Indeed, the discoveries of Myriad and some of the other defendants likely were a result of the post-*Chakrabarty* era which lead to the exponential growth of the biotechnology industry in the United States. Such discoveries are incentivized by the patent system's grant of an exclusivity period. But for such a reward system, investors are unwilling to

invest in the costly research and development needed to make products like Myriad's available to those who need them.

28. Plaintiffs contend that patents related to isolated DNA molecules run afoul of § 101. *MF*s ¶ 96; Pl. Br. at 20-26; Sulston Decl. ¶¶ 26-27. To support their position, Plaintiff cite the Bermuda Principles and state that"[a]ll human genomic sequence information should be freely available and in the public domain" to encourage research and development. Sulston Decl. ¶ 33. Yet, I am not aware of any therapeutic or diagnostic product that has been made available to the public as a result of such data sharing. In contrast, numerous diagnostics and therapeutic products protected by patents have entered the commercial market place.

A. NATURAL PRODUCTS THAT HAVE BEEN ISOLATED AND PURIFIED ARE ELIGIBLE FOR PATENT PROTECTION

29. In each of the following cases patentability was upheld because the compositions sought to be patented were isolated and purified. Those compositions, or compounds, did not exist in nature or the prior art in pure form, as claimed in the subject patents.

30. In a seminal case, *Parke-Davis & Co. v. H. K. Mulford Co.*, Judge Learned Hand held valid a patent on an adrenalin compound isolated and purified from the suprarenal glands of certain animals. 189 F. 95, 103 (S.D.N.Y. 1911). In *Parke-Davis,* it had been known that suprarenal gland in powdered form had "hemostatic, blood pressure

raising and astringent properties" but could not be used for those purposes in gross form. The patentee isolated and purified adrenaline having the desired characteristics in pure and stable form. The new composition of matter differed from the prior art extracts "in kind" -- not merely in "degree of purity." *Id.* at 103. Further, the change in the new composition resulted in "ample practical differences." *Id.* The court held that

> "even if [the adrenaline] were merely an extracted product without change, *there is no rule that such products are not patentable.* [The Patentee] was the first to make [adrenaline] available for any use by removing it from the other gland-tissue in which it was found, and, *while it is of course possible logically to call this a purification of the principle, it became for every practical purpose a new thing commercially and therapeutically.* That was a good ground for a patent."

Parke-Davis, 189 F. 95 at 103 (emphasis added).

31. In *Merck*, at issue was a patent on "Vitamin B_{12}-Active Composition" useful for treating pernicious anemia. *Merck & Co., Inc. v. Olin Mathieson Chem. Corp.*, 253 F.2d 156, 157-158 (4th Cir. 1958), *cited with approval in In re Kratz*, 592 F.2d 1169, 1174 (C.C.P.A. 1979). Vitamin B_{12} "is produced in minute quantities in the bodies of cattle." *Id.* at 161. Such naturally occurring Vitamin B_{12} has "some therapeutic and commercial value, but the great superiority of the patented composition is clearly established." *Id.* Patentees obtained the claimed Vitamin B_{12} compositions from the

microorganism, *Lactobacillus lactus*. The court held that that patented compositions satisfied the novelty and utility requirement. The Court reasoned that "[t]he active substance was *unidentified and unknown*" prior to the patentee's invention. *Id.* at 163 (emphasis added). But, the purification step from the naturally occurring product was one "from complete uselessness to great and perfected utility" and hence was "no mere advance in the degree of purity of a known product." *Id.* at 164.

32. The Court's holding in *Merck* was premised on the statutory language of the 1952 Patent Act. As the Court properly noted, "[t]here is nothing in the language of the Act which precludes the issuance of a patent upon a 'product of nature' when it is a 'new and useful composition of matter' and there is compliance with the specified conditions for patentability." *Merck*, 253 F.2d at 161.

33. *In re Bergstrom* dealt with the prostaglandins PGE2 and PGE3, extracted from human or animal prostate glands. 427 F.2d 1394, 1397 (C.C.P.A. 1970). The patent examiner had rejected the claims, reasoning that "inasmuch as the 'claimed compounds are naturally occurring' . . . they therefore 'are not 'new' within the connotation of the patent statute.'" *Id.* at 259. *Bergstrom* is precedential and binding in the instant case as it is from the Court of Customs and Patent Appeals ("CCPA") – the predecessor to the current Federal Circuit. *South Corp. v. U.S.*, 690 F.2d 1368, 1370 (Fed. Cir. 1982) (adopting CCPA body of law). The claimed compositions occurred inherently in "nature," *i.e.*, in sheep prostate glands and in previously known crude extracts of those glands. The court reversed the Patent Office and

explained the error:

> "what appellants claim--pure PGE2 and PGE3--is not 'naturally occurring.' Those compounds, as far as the record establishes, do not exist in nature in pure form, and appellants have neither merely discovered, nor claimed sufficiently broadly to encompass, what has previously existed in fact in nature's storehouse, albeit unknown, *or* what has previously been known to exist."

Bergstrom, 427 F.2d. at 1401 (emphasis in original).

34. Another precedential case, *In re Kratz*, related to the naturally occurring chemical, 2-methyl-2-pentenoic acid ("2M2PA"), a chemical responsible for the characteristic flavor of strawberries. 592 F.2d 1169 (C.C.P.A. 1979). Tellingly, Plaintiffs never cite *Kratz*, in spite of its precedential value. Kratz and Strasburger were the first to establish the presence of 2M2PA in strawberries and to discover that when 2M2PA was added to foodstuffs, it imparted a strawberry flavor and aroma. Their claim to 2M2PA in "substantially pure" form was upheld even though "2M2PA is a naturally occurring constituent of strawberries and is not 'per se' novel," "since the claims do not encompass natural compositions in that 'substantially pure' 2M2PA does not apparently occur in nature." *Id.* at 1174.[1]

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[1] In a case decided with *Chakrabarty* by the lower court, *In re Bergy*, a claim to a "biologically pure culture of Streotomyces vellosus" was held not to be a "product of nature," contrary to the examiner's position, and patent eligible under § 101. 596

B. NO CASE STANDS FOR THE PROPOSITION THAT NATURAL PRODUCTS ARE NOT PATENT-ELIGIBLE

35. On careful analysis, the kind the Solicitor's Office conducted prior to issuing the 1995 Guidelines, it becomes clear that patentability was denied in the following cases because the composition sought to be patented was known and used from time immemorial – *not* because the products were naturally occurring.

36. In *Am. Wood-Paper Co. v. Fibre Disintegrating Co.*, 90 U.S. 566 (1874), cellulose had been obtained from various sources, including rags, straw, wood and other vegetable substances in the paper industry. 90 U.S. at 594-95. The patent at issue related to cellulose derived from wood pulp by a new process. Patentee claimed "a pulp *suitable* for the manufacture of paper, made from wood or other vegetable substances." *Id.* at 577 (emphasis added). The pulp which had been in common public use prior to the patentee's alleged invention, was "undeniably also cellulose, *suitable for manufacturing paper*, and so far as appears, *equally suitable*." *Id.* at 594 (emphasis added). Thus, the court noted that "[t]he *substance of the products . . . , was the same, and so were their uses*." *Id.* (emphasis added). The court held that "[p]aper-pulp obtained from various vegetable substances was in common use before the

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F.2d 952, 972, 987 (CCPA 1979). On certiorari, the Supreme Court held Chakrabarty's microorganisms patent eligible under § 101 but did not address the *Bergy* case, as it had become moot. *See Chakrabarty*, 447 U.S. at 307.

original patent was granted [to patentee], and whatever may be said of their process for obtaining it, the product was in no sense new." *Id.* at 596. Thus, the patent was "void for want of *novelty* in the manufacture patented." *Id.* (emphasis added).

37. In *Cochrane v. Badische Anilin & Soda Fabrik*, alizarine was a known compound that had been extracted from the roots of madder plant and used in the dye industry. 111 U.S. 293 (1884). The Supreme Court held that the artificial alizarine, synthetically produced was not patentable because "[i]t was an old article," *i.e.*, it was the same chemical composition as alizarine previously extracted from madder root that had been used from "time immemorial" for dyeing. *Id.* at 311-12.

38. *Ex parte Latimer* involved cellulose fibers, a "well known material" which had been used from "time immemorial" in the textile industry. 1889 Dec. Comm'r Pat. 123, 125 (1889). The patentee developed a process for isolating the fibers from pine needles. The court noted, " [f]iber, whether of plants – such as hemp, flax, cotton -- or of the leaves of trees – such as the [pine tree] -- or of the wood of trees and shrubs, is a well known material ... It has been employed from time immemorial in the manufacture of threads, cordage, fabrics and textiles..." *Id.* The court found that the claimed fiber isolated from its natural matrix was the "*same* thing" having the "*same* construction" as prior art fiber used in the textile industry and no different from its naturally occurring counterpart. *Id.* (emphasis added). The Patent Commissioner held that the patentee had failed to make any "discovery" since the fibers claimed were not a "new' and useful product. *Id.* at

125-26.

39. *Gen. Elec. Co. v. De Forest Radio Co.* related to tungsten, an "old product" which had been isolated since at least the early 1700s and had been used in metallurgy ever since. 28 F.2d 641 (3d. Cir. 1928). The oxide of tungsten (WO_3) found in the earth. is brittle, whereas pure or substantially pure tungsten is highly ductile. The patentee developed a process to convert tungsten oxide to pure tungsten. The court found that the claimed tungsten of high ductile strength was not patentable because it was *not new* at all. *Id.* at 643.

40. *In re Marden*, 47 F.2d 957 (C.C.P.A. 1931) ("*Marden* I") related to uranium, which had been discovered in 1789 and its properties had been "well known for many years." Patentee claimed uranium as a "new article," including some of its properties. The court held there was "nothing new" or "inventive" and thus denied patent protection. *Id.* at 957-58.

41. Similarly, in *In re Marden*, 47 F.2d 958 (C.C.P.A. 1931) ("*Marden* II") pure vanadium had been known for years in the metallurgy industry. Patentee attempted to obtain patent rights to not only methods for preparing vanadium in ductile form but also pure, ductile vanadium. The court denied patent protection and held that "pure vanadium is *not new in the inventive sense*." *Id.* at 959 (emphasis added).

42. The patent at issue in *Funk Bros. Seed Co. v. Kalo Inoculant Co.* related to inoculants of the bacteria genus Rhizobium. 333 U.S. 127 (1948). These bacteria infect the roots of leguminous plants

and form nodules that allow the plants to fix nitrogen from the air (*i.e.*, a fertilizer). Different species of the bacteria were effective for different types of plant crops. Prior to the patent at issue, manufacturers packaged and sold single species inoculants. *Id.* at 129. A few mixed cultures were sold but they had been "generally unsatisfactory," because different species produced an inhibitory effect on each other. *Id.* The patentee discovered six strains of species of the bacteria that were mutually non-inhibitive, and capable of inoculating several groups of plants.[2] *Id.* at 130. The claims, however, were not limited to the six strains. Rather, they were directed to an inherent natural property of an unspecified mixture of old products. The Supreme Court recognized that the mixture covered by the claims was a new composition but denied the patent because it found the combination of bacteria to be an obvious combination of known, commercially available products. *Id.* at 131-32.

III. MYRIAD'S COMPOSITION OF MATTER CLAIMS COMPLY WITH THE PATENT LAWS

43. I reviewed claims 1, 2, 5, 6, and 7 of the '282 patent; claim 1 of the '473 patent; and claims 1, 6, and 7 of the '492 patent. These claims all relate to isolated DNA molecules comprising either the

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[2] Jackson misstates the basic facts of the case, reflecting his lack of experience in precise legal case analysis. Funk Brothers was not denied a patent. Bond, the patentee was. Further, the bacteria disclosed in *Funk*, was not a "weed killer," rather it was a fertilizer. Jackson Decl. ¶ 32.

*BRCA*1 or *BRCA*2 DNA -- molecules that fall squarely under the statutory category "composition of matter."[3] For ease of reference I will refer to such claims as the "isolated DNA" claims.

44. The term "isolated" is expressly defined in the patent specification of the Myriad patents. *See, e.g.*, '473 patent at col. 19:6-15. The patent states that an "isolated" or "substantially pure" nucleic acid (*e.g.*, an RNA, DNA or a mixed polymer) is one which is substantially separated from other cellular components which naturally accompany a native human sequence or protein, *e.g.*, ribosomes, polymerases, many other human genome sequences and proteins. The term embraces a nucleic acid sequence or protein which has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems. In other words, DNA molecules that have been excised and extracted from cells or chemically synthesized.

45. The claimed isolated *BRCA*1 and *BRCA*2 DNA molecules of the Myriad patents are chemical compositions that have a specific utility, *e.g.*, molecular diagnostics. These DNA molecules, like all other DNA molecules, are chemical compounds consisting of a chain or strand of four different types

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[3] *Chakrabarty*, 447 U.S. at 309 ("'composition of matter' has been construed consistent with its common usage to include 'all compositions of two or more substances ... and all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders, or solids.'") (citations omitted).

of nucleotides, i.e., adenine ("A"), cytosine ("C"), guanine ("G") and thymine ("T"). These bases are linked together through the sugar phosphate backbone. These four letters of the alphabet are used as a shorthand scientific notation to represent the chemical composition of the DNA molecule. Indeed, shorthand notation, such as letters of the alphabet, are frequently used to name chemical compounds and is not a practice exclusive to DNA molecules. For example, prostaglandin is designated as PGE; Vitamin B12 is designated as $C_{63}H_{87}CoN_{14}O_{14}P$; and the polymer polypropylene is designated as PPE.

46. All chemical compounds inherently carry information. DNA molecules are no different. Indeed, the information in a chemical compound is dictated by its chemical, physical and structural properties. These inherent properties mandate the functionality of the chemical entity. Like any other chemical compound, DNA molecules in general and the claimed *BRCA*1 and *BRCA*2 DNAs at issue here, may be patent eligible if all conditions for patentability are met. The mere fact that the DNA molecules of the invention inherently carry information is not a bar to patentability.

47. Under the patent statutes and case law interpretation of those statutes, "isolated and purified" DNA molecules are patent eligible subject matter on multiple grounds. First, an excised gene or synthetic DNA is eligible for patent protection either as a "composition of matter" or as "an article of manufacture" – categories of patentable subject matter specifically enumerated by § 101. Second, "isolated" DNA molecules do not occur in nature and are different from the complex naturally occurring

native DNA. *See* the legal analysis in the 2001 Guidelines, discussed *supra* at ¶ 18.

48. "Isolated" DNA molecules are structurally and functionally distinct from their naturally occurring counterpart in the human body. The environment of a DNA molecule dictates not only its structure but also its function (what it does). DNA in the human body is an integral part of chromosomes. In the chromosomal structure, DNA is typically present with proteins bound and highly regulated in its native environment. When DNA is no longer in its native environment, its expression can be regulated by artificial mechanisms. In addition, complementary DNA ("cDNA") is completely artificial as admitted by Plaintiffs (MF ¶ 62; Mason Decl. ¶ 29), and is structurally distinct from chromosomal DNA in that, among other differences it contains no intronic sequences and is not associated with proteins. cDNA is also functionally distinct from chromosomal DNA in that it does not contain regulatory sequences; it can serve as a template for mRNA synthesis; and it can be used as a diagnostic tool in this "isolated" form. Additionally, functions of genes as they occur naturally are not completely understood. Plaintiffs' attempt to equate the function of isolated genes to that of their naturally occurring counterparts is simply trivializing the complexity of the scientific principles at issue in this case.

49. Myriad's isolated DNA claims are directed to compositions of matter and thereby patent eligible subject matter under 35 U.S.C. § 101. The patent eligibility of the isolated DNA claims of the Myriad patents is fully supported by binding precedent of the

Supreme Court, the Federal Circuit, and the CCPA. Moreover, patenting compositions or compounds isolated from nature follows well-established legal precedence and was by no means a new practice at the USPTO. *See the discussion supra* at ¶¶ 30-34 re *Parke-Davis, Merck, Bergstrom*, and *Kratz*. In 1980, the Supreme Court held that "anything under the sun that is made by man" is patent eligible, consistent with these earlier cases. *Chakrabarty*, 447 U.S. at 309.

V. PLAINTIFFS MISINTERPRET THE CASE LAW ON THE PATENT ELIGIBILITY OF ISOLATED AND PURIFIED NATURAL PRODUCTS

50. Plaintiffs attempt to distinguish *Parke-Davis*, denigrate *Merck* and *Bergstrom* and omit any discussion of *Kratz*. *MF* ¶¶ 117, 119; Pl. Br. at 24-25 Jackson ¶¶ 26-31, 35-37. In my opinion, these cases are directly analogous to the instant case.

51. Like the purified adrenaline of *Parke-Davis*, the isolated DNA molecules of the Myriad claims are different "in kind" from naturally occurring counterparts. The isolated DNA molecules claimed in Myriad's patents are distinct functionally and structurally from the naturally occurring *BRCA* genes, allowing the claimed compositions to be used for a practical new purpose, *e.g.*, diagnostics, which can only be achieved by virtue of the isolation and purification of the molecule. The isolated DNA molecules of the Myriad patents become "a new thing commercially" and thus patentable under the rubric of *Parke-Davis*.

52. Plaintiffs contend that *Parke-Davis* is not

analogous to the claims in the Myriad patents, relying on Jackson ¶¶ 26-31 (*MF* ¶ 117, Pl. Br. at 25; Jackson Decl. ¶¶ 26-31). Jackson states: "The human body does not possess a natural process for purifying adrenaline as it does for isolating and splicing together genes. Genes and their splicing occur naturally, without human intervention; purified adrenaline does not." Jackson Decl. ¶ 29. This position is factually incorrect. The human body does not have *any* natural mechanism for isolating and splicing genes. Rather, splicing to remove introns (present in DNA molecules) is a modification of RNA molecules – not DNA molecules. *See* Jackson Decl. ¶ 28. *See also, e.g.*, Lehninger, PRINCIPLES OF BIOCHEMISTRY 1008-11 (4th ed. 2005).

53. If anything, the human body possesses a natural mechanism for "isolating" adrenaline by virtue of secretion of this hormone into the blood stream. Genes are not secreted by cells in the body, nor are they naturally isolated by the body. Genes remain intact in the nucleus. The isolation of genes or any DNA through molecular biological techniques requires cell disruption and chemical cleavage to remove the DNA from the chromosome, or chemical synthesis and amplification of synthetic DNA.

54. Just as the patentee in *Parke-Davis* provided a new use for adrenaline (*i.e.*, hemostatic, blood pressure raising and astringent properties) by its isolation and removal of gland tissues, here too, Myriad has provided an entirely new utility for the isolated *BRCA*1 and *BRCA*2 DNA, *i.e.*, diagnostics, as compared to their naturally occurring counterparts which are incapable of performing this function.

55. In *Merck*, the court concluded: "No one had produced even a comparable product" to the product at issue in the case and there was no novelty bar to the product claimed. 253 F.2d at 162. The same is true in this case. Like the situation in *Merck*, Myriad's patented compositions, *i.e.*, DNA molecules covering *BRCA*1 and *BRCA*2 nucleotides, were previously "unidentified and unknown" prior to being disclosed in the Myriad patents, and it was their very isolation from the chromosomal DNA environment which rendered them useful as a diagnostic.

56. The court in *Merck* rejected defendant's argument that "anyone skilled in the field searching for a new B vitamin would turn to the known sources of other B vitamins." 253 F.2d at 161. The court emphasized that this argument "assumes knowledge of which the scientific world was ignorant until the work of the patentee was done." *Id.* Similarly, here, just because the DNA encoding the *BRCA*1 and *BRCA*2 genes are necessarily present in chromosomal DNA does not preclude patenting the newly identified, isolated genes and their function.

57. Plaintiffs attempt to distinguish *Merck* from the instant case. *MF* ¶ 119, Pl. Br. at 24-25; Jackson Decl. ¶ 37. Yet, Plaintiffs' analysis is flawed. Like the Vitamin B_{12} compositions at issue in *Merck*, the isolated *BRCA*1/*BRCA*2 DNA molecules of the Myriad patents have "never existed before; there was nothing comparable to them." 253 F.2d at 164. Indeed, it was the inventors' discovery of the structure and function of the *BRCA1* and *BRCA2* genes that revealed their actual, practical, "real world" utility. In their "natural" form, the *BRCA*1/*BRCA*2 DNA molecules of the Myriad

patents, like the "natural" Vitamin B_{12} compositions of *Merck*, are quite "useless" for the intended utility of the invention (*i.e.*, diagnostics in the instant case).

58. Like the chemical compounds at issue in *Bergstrom*, the isolated and purified *BRCA*1/*BRCA*2 DNA molecules are eligible for patent protection when isolated from their natural state and purified. As the court in *Bergstrom* noted, "pure materials necessarily differ from *less* pure or impure materials and, if the latter are the only ones existing and available as a standard of reference, ... perforce the 'pure' materials are 'new' with respect to them." 427 F.2d. at 1402 (emphasis in original). Moreover, the mere existence of *BRCA*1/*BRCA*2 DNA as part of the chromosomal DNA does not negate the novelty or patentability of the isolated and purified *BRCA*1/*BRCA*2 DNA molecules. *See id.* ("*The existence of a compound as an ingredient of another substance does not negative novelty in a claim to the pure compound*, although it may, of course, render the claim unpatentable for lack of invention [*i.e.*, the predecessor test for obviousness under Section 103]...") (quoting *In re Williams*, 171 F.2d 319 (C.C.P.A. 1948) (emphasis in original).

59. As in *Kratz*, the claimed isolated DNA molecules of the Myriad patents do not cover *natural* compositions because the isolated DNA molecules are distinct in form and kind from their naturally occurring counterparts. *Supra* ¶ 34.

60. Plaintiffs have not – because they cannot – point to a single case standing for the proposition that natural products are not patent eligible *per se*. Rather, to support their position that the isolated DNA molecules of the Myriad patents are not eligible

for patent protection. Plaintiffs rely on a line of cases in which the court found known, old products or commercially available products unpatentable. *MFs* ¶¶ 115-123; Pl. Br. at 21-24; Jackson Decl. ¶¶ 7-16 (citing *Cochrane & Others v. Badische Anilin & Soda Fabrik*, 111 U.S. 293 (1884)); ¶¶ 17-25 (citing *Am. Wood-Paper Co. v. Fibre Disintegrating Co.*, 90 U.S. 566 (1874)); ¶¶ 38-40 (citing *Gen. Elec. Co. v. De Forest Radio Co.*, 28 F.2d 641 (3d. Cir. 1928)); ¶¶ 32-24; ¶¶ 32-34 (citing *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948)); *see also* Pl. Br. at 31 (citing *Marden* I and *Marden* II).

61. These are the very cases I reviewed when I was the Solicitor in addressing the patent eligibility of biotechnology inventions under § 101 for Commissioner Lehman. See my discussion of these cases *supra* at ¶¶ 35-42.

62. Plaintiffs' reliance on these cases is misplaced for at least two independent reasons. First, in each case, the composition sought to be patented was old – in that it was commercially available or known in the art. These cases primarily turn on whether the products at issue met the "novelty" or non-obviousness statutory requirements. Second, these cases have marginal precedential value as they were issued pre-1952 Patent Act, which is the relevant legal standard of analysis.

63. In *Cochrane*, the court's holding of invalidity of the reissue patent was based, in part, on the fact that artificial alizarine synthetically produced was *identical* in its properties and composition to alizarine previously produced by other methods. *Cochrane*, 111 U.S. at 300-301. Similarly, the pulp product claimed in *Wood-Paper* had been in common

public use and the court's holding turned on the "novelty" statutory requirement. *Wood-Paper*, 90 U.S. at 596. Finally, the Patent Commissioner's refusal to grant patentee's application was because the pine needle fibers in *Latimer* were essentially the *same* cellulose fibers that had been known and used in the manufacture of threads, cordage, fabrics and textiles. *Latimer*, 1889 Dec. Comm'r Pat. at 125. *See also*, *Marden* I, 47 F.2d 957 and *Marden* II, 47 F.2d 958 (rejecting patentability where the product was not "new" or "inventive").

64. Unlike the situation in *Cochrane*, *Wood-Paper*, *Latimer*, *Marden* I and *Marden* II, it is undisputed that the isolated DNA molecules coding for the *BRCA1* and *BRCA2* genes were *not* known prior to the invention disclosed in the Myriad patents. Indeed, it was the discovery of the location, structure and function of the *BRCA1* and *BRCA2* genes that was a fundamental breakthrough for the development of cancer diagnostics and therapeutics, warranting patent protection. Additionally, as explained *supra* (¶¶ 29-34), the isolated DNA molecules covered by the patent-in-suit are by no means "identical" to their naturally occurring counterparts and are in fact distinct – chemically, structurally and functionally. Thus, application of *Cochrane*, *Wood-Paper*, *Latimer*, *Marden* I and *Marden* II to this case carries no force.

65. The same holds true for *General Electric* In *General Electric*, the issue of patentability of tungsten turned on the "novelty" requirement. As the court properly noted, the patentee had not sought a patent for a "new" composition of matter. Rather, patentee had claimed a product that later proved to

be tungsten – an old product. 28 F.2d at 641.

66. *Funk* is equally inapplicable to the instant case. The claim at issue in *Funk* was not for a true "product of nature." The claimed mixed culture did not exist in natural form and thus, contrary to Plaintiffs' representations (*MFs* ¶ 118, Pl. Br. at 21-22, 26; Jackson Decl. ¶ 32-34), *Funk* does not stand for the proposition that products of nature are not patentable. Instead, the *Funk* decision is more appropriately directed to non-obviousness or pre-1952 Patent Act "invention" requirement and not to the statutory classes of patent eligible subject matter. The court's decision turned on obviousness of the claimed product as a combination of old, commercially available products. Each of the individual strains of each bacterial species had been commercially available prior to the patent-in-suit. The court admitted that one could patent "the application of the law of nature to a new and useful end" but held that the "aggregation of species fell short of invention ... [i.e., was obvious]... within the meaning of the patent statutes" because the mixed culture performed no new function other than that of convenient packaging. *Funk*, 333 U.S. at 130-31.

67. In his concurring opinion, Justice Frankfurter urged caution with respect to the majority's use of the phrases "works of nature" and "laws of nature":

> It only confuses the issue . . . to introduce such terms as 'the work of nature' and the 'laws of nature.' For these are vague and malleable terms infected with too much ambiguity and equivocation. Everything that happens may be deemed 'the work of nature,' and

> any patentable composite exemplifies in its properties 'the laws of nature.' Arguments drawn from such terms for ascertaining patentability could fairly be employed to challenge almost every patent. On the other hand, the suggestion that 'if there is to be invention from such a discovery, it must come from the application of the law of nature to a new and useful end' may readily validate [patentee's] claim. Nor can it be contended that there was no invention because the composite has no new properties other than its ingredients in isolation. [Patentee's] mixture does in fact have the new property of multi-service applicability.

333 U.S. at 134-35.

68. Further, the claims at issue in *Funk* did not define the composition (i.e., the combination of the six strains). Rather, the claims were directed to an inherent natural property of an unspecified mixture of old products. As indicated in Justice Frankfurter's concurrence, had the claims actually been directed to the strains which were mutually non-inhibitory, the outcome of the case might have been different. Indeed, notwithstanding his objections, Justice Frankfurter, in his concurring opinion, ruled to invalidate the patent on the ground that the product claim was too broad. The claim was for any mixture of compatible strains and did not adequately identify the particular strains that the patentee had discovered. *Funk*, 333 U.S. at 133.

69. Plaintiffs' improper application of *Funk* to the

present case is premised on the misunderstanding that "[p]atented genes can, and normally do serve the ends nature originally provided." Jackson Decl. ¶ 34 (relying on *Funk*, 333 U.S. at 131). But, as explained above, isolated and purified genes, such as those claimed in the Myriad patents do *not* "serve the ends nature originally provided" because they are distinct structurally and functionally by virtue of their isolation.

70. Plaintiffs' application of these cases is additionally flawed because it is premised on a fundamental misconception and misunderstanding of how to apply basic principles of patent law and policy to biotechnological inventions. *MFs* ¶ 58-59, 62-63, 65, 113-114; Pl. Br. at 20-28; Jackson Decl. ¶ 12-15, 30-34. For example, Jackson disputes the scientifically based principle that DNA and genes are chemicals and "should be analyzed for patent purposes in the same manner as other chemicals." Jackson Decl. ¶ 12. Jackson is wrong. DNA *is* a chemical composition. A DNA molecule is a chain or strand of four different types of bases, i.e., adenine, cytosine, guanine, and thymine and, these bases are linked together via a sugar-phosphate backbone. Thus, a DNA molecule is a combination of basic chemical elements, *i.e.*, oxygen, nitrogen, carbon, phosphate. By any definition, DNA falls squarely within what is considered a chemical composition.

71. A concern voiced by Plaintiffs in treating genes as chemical entities is that the "threat of the patentee locking up a substance and all its uses is far greater with gene patents than with chemicals dues to the science of genes." Jackson Decl. ¶ 15. *See also MF* ¶ 114; Pl. Br. at 36-37. Dr. Jackson reasons that

while one can readily invent around chemical molecules "by creating either a slightly different method of synthesis or a minor variation of the patented (or natural) substance," one "cannot invent around a gene, potentially allowing patents holders to enjoy a monopoly, thereby hampering further downstream diagnostic and therapeutic research." Jackson Decl. ¶ 15. Plaintiffs, in essence, imply that the grant of an exclusionary patent right is wrong. *MFs* ¶ 125-141, Pl. Br. at 6, 35, Jackson Decl. ¶ 13, 15. In fact, the right to exclude others from practicing a claimed invention is the very essence of the patent right. *See* 35 U.S.C. § 271. Thus, the ability to invent around an invention frustrates that right. If a pioneering invention, such as that covered by the Myriad claims, is properly claimed, those claims should prevent "inventing around" and allow the inventor to fully benefit from the exclusionary rights granted by the patent. By granting exclusionary rights, the patent system promotes making improvements on the claimed invention and permits others to practice the claimed invention after the patent expires. In contrast, if another party can invent around the claimed invention and reap the benefits of the patentee's discovery, the patentee's ability to recoup and benefit from its investment are frustrated.

72. Indeed, these very concerns were raised prior to the implementation of the 2001 Guidelines. *See e.g.*, Letter from R. Rodney Howell, President, Association for Molecular Pathology to Commissioner, USPTO (March 20, 2000), *available at* http://www.uspto.gov/web/offices/com/sol/comments/utilguide/acmg.pdf ; Letter from Debra G.B. Leonard,

President, Association for Molecular Pathology to Commissioner, USPTO (March 17, 2000), *available at* http://www.uspto.gov/web/offices/com/sol/comments/utilguide/amp.pdf. As the USPTO recognized such concerns are unfounded. When a patent claiming a new chemical composition issues, the patentee has the right to exclude others from making, using, offering for sale, selling, or importing the composition for a limited time. 35 U.S.C. § 154. In exchange for this limited exclusionary right, the patentee is required to disclose only one utility, that is -- teach others how to use the invention in at least one way – as long as the utility is specific, substantial and credible. *See* the 2001 Guidelines, cited *supra* at ¶ 18. The patentee is *not* required to disclose *all possible uses*. In fact, promoting the subsequent discovery of other uses – uses that can be patented if they meet the statutory requirements -- is one of the benefits of the patent system.

73. Accordingly, when patenting is made available for genes as it is for other chemical compositions, progress is promoted for at least four independent reasons. First, the claimed invention is fully disclosed to those working in the field and thus made fully available after the limited exclusionary period (here, in 2014) instead of being held as a trade secret. Second, the original inventor has the ability to obtain financial support to recoup research and development costs. Third, a new chemical composition is made available as a basis for future research. Other inventors are incentivized to develop new uses for the patented composition and have the opportunity to patent those uses, if the patent statutes are met. Last but certainly not least, a new and nonobvious invention (here, a diagnostic tool) is

provided for those who need the invention (here, diagnosis of a propensity toward contracting breast and ovarian cancer).

74. Thus, Plaintiffs' concerns are unsupported by the underlying principles of patent law and policy. Since *Chakrabarty*, the biotechnology industry has flourished at an exceptional rate in the United States by virtue of the patent system. The United States has emerged as a leader in the biotechnology industry serving as a role model for other countries striving to compete in this industry. Indeed, the post-*Chakrabarty* patent system has been critical to the growth and competitiveness of American biotechnology because, among other reasons, investors simply expect a company to have its intellectual property protected. Thus, the promise of patent protection attracts capital that the biotechnology industry requires to survive.

75. Most, if not all, of the life saving inventions available world-wide would never have been discovered, developed and commercialized but for the potential profits afforded by the exclusive rights granted by the patent system. In this case, Myriad probably would not have -- because it could not have -- spent the capital necessary for the research and development that led to the ground-breaking discoveries of the *BRCA1* and *BRCA2* genes and ultimately to their commercialization had it not been for the exclusive rights granted by the patent system. Those rights provided Myriad with the possibility of recouping its costs and reaping the benefits of its discoveries.

76. Moreover, Plaintiffs' flawed analysis of the case law is premised on a misunderstanding of basic

scientific principles. *MFs* ¶ 48, 58-60, 62, 65, 114, 117; Pl. Br. at 4-5, 20, 26-27; Jackson Decl. ¶¶ 25, 29, 31. For example, like adrenaline, vitamin B12 and/or 2M2PA where patentability was upheld (*supra* ¶¶ 30-34), DNA, too, is a chemical composition (¶¶ 43-46). It thus requires application of the same patentability analysis as do other chemical compositions. Further, all chemical compositions inherently carry "information" in that the nature of the atoms in the composition, their arrangement, and their environment dictates their function. DNA is no different. *Compare with* Jackson Decl. ¶ 20. The "information" inherent in any chemical composition is dictated by the laws of nature through its inherent chemical, physical and structural properties. These inherent properties of a chemical entity mandate its functionality, including for example, its chemical reactivity, catalytic properties, and biological interactions. The same holds true for DNA. For example, the transcription of a gene into mRNA consists merely of a series of well-orchestrated chemical reactions that are being dictated by the inherent properties of the DNA molecule.

77. Finally, *American Fruit Growers v. Brogdex Co.*, 283 U.S. 1 (1931) does not support Plaintiffs' unsubstantiated "legal principle" that "natural products" are not patentable *per se*. The Court's holding in *American Fruit Growers* was not predicated on the borax treated fruit being a "natural product." Rather, the Court used this opportunity to define what constitutes an "article of manufacture"[4]

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[4] *American Fruit Growers*, 283 U.S. 1, 11 (1931) ("manufacture' means "the production of articles for use from raw or prepared

and held that the borax treated fruit was not. In contrast, the isolated DNA molecules of the Myriad patents fall squarely within the Court's definition of an "article of manufacture." The *BRCA1/BRCA2* DNA molecules are isolated from cells, *i.e.*, substantially separated from other cellular components which naturally accompany a native human sequence or protein, *e.g.*, ribosomes, polymerases, many other human genome sequences and proteins. *See, e.g.*, '473 patent, col. 19:6-15; '282 patent, col. 19:8-18; and '492 patent, col. 17:62 – col. 18:5. By virtue of this "isolation" they are necessarily "transformed" under *American Fruit Growers*. In other words, the claimed DNA molecules are produced from raw materials (the naturally occurring gene or the chemical molecules that make up the claimed DNA) in a "new and different" form that does not occur in nature -- a form that provides the basis for a diagnostic tool (i.e., a new property).

VI. MYRIAD'S METHOD CLAIMS ARE PATENT ELIGIBLE UNDER *BILSKI* AND ITS PROGENY BECAUSE THEY ALL HAVE A "TRANSFORMATIVE" STEP CENTRAL TO THE PURPOSE OF THE CLAIMS

78. In addition to assessing the requirements of patentability of biotechnology inventions, Commissioner Lehman charged me with clarifying the legal requirements for statutory subject matter

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materials by giving to these materials new forms, qualities, properties, or combinations, whether by hand-labor or by machinery"), *quoted with approval in Chakrabarty*, 447 U.S. at 309.

with regard to computer-related inventions. This initiative led to the Examination Guidelines for Computer-Related Inventions (61 Fed. Reg. 7478 (1996) (legal analysis reproduced in MPEP § 2106 (July 1998)), and involved the analysis of all the cases cited by Plaintiffs relating to such subject matter. *See* Jackson ¶¶ 43-48. *MFs* ¶ 122-124; Pl. Br. at 26-29. Specifically, these cases addressed whether the subject matter sought to be patented was an "abstract idea" precluding patentability.

79. I will discuss these cases as they pertain to the "method claims" at issue in this case. Specifically, I have reviewed claim 20 of the '282 patent; claim 1 of the '999 patent; claim 1 of the '001 patent; claim 1 of the '441 patent and claims 1 and 2 of the '857 patent. These claims are collectively referred to as the "method claims."

80. I understand that Plaintiffs contend that these claims run afoul of *Bilski* and its progeny because they purportedly cover mental steps and abstract ideas. Pl. Br. at 29-30 n.9 (citing *In re Bilski*, 545 F.3d 943, 954(Fed. Cir. 2008), *cert. granted*, 129 S. Ct. 2735 (2009)). For the reasons discussed below, I disagree.

81. Out of the at least 25,000 genes now identified, Myriad discovered that mutations in the *BRCA*1 or *BRCA*2 gene are correlated with breast and/or ovarian cancer -- a discovery Myriad scientists were first to make. Based on this discovery, Myriad invented and claimed certain diagnostic methods for detecting whether a patient has the mutation.

82. Each of Myriad's method claims requires analyzing a sequence of the *BRCA* gene from a human tissue or tumor sample. To do so, the DNA[5] must be isolated from the sample and sequenced prior to identifying variations in the DNA.

83. Whether the method is for "detecting a germline alteration" (*e.g.*, claim 1 of the '999 patent), for "screening" for an "alteration" (*e.g.*, claim 1 of the '001 patent and claim 20 of the '282 patent), "for identifying" a "mutant nucleotide sequence" (*e.g.*, claim 1 of the '857 patent), or for "diagnosing a predisposition for breast cancer" (*e.g.*, claim 2 of the '857 patent), the claimed method cannot be conducted while the DNA is in its naturally occurring state.[6]

84. Furthermore most of the method claims involve additional transformations. For example, claim 20 of the '282 patent reads:

> 20. A method for screening potential cancer therapeutics which comprises: *growing* a transformed eukaryotic host cell containing an altered BRCA1 gene causing cancer in the presence of a compound suspected of being a cancer therapeutic, *growing* said transformed

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[5] For simplicity, I use the term "DNA" to describe what molecule is analyzed. In fact, its corresponding RNA or cDNA can be used for the analysis.

[6] For simplicity, I use the word "detecting" to include "screening," "identifying," and "diagnosing," the various terms used in the patents-in-suit.

> eukaryotic host cell in the absence of said compound, *determining* the rate of growth of said host cell in the presence of said compound and the rate of growth of said host cell in the absence of said compound and *comparing* the growth rate of said host cells, wherein a slower rate of growth of said host cell in the presence of said compound is indicative of a cancer therapeutic.

'282 patent at col. 156:15-27 (emphasis added).

Each of the italicized actions involves a transformation ("growing") or requires a machine to perform the claimed step ("determining" and "comparing"). These latter steps cannot be performed in the absence of a machine. *See Prometheus Labs. v. Mayo Collaborative Servs.*, 581 F.3d 1336, 1347 (Fed. Cir. 2009) ("Some form of manipulation, such as the high pressure liquid chromatography method specified ... is necessary to extract the metabolites from a bodily sample and determine their concentration.")

85. Myriad's method claims are in many ways analogous to those in *Prometheus*. *See, e.g. Prometheus*, 581 F.3d 1347-50 (discussing claims 46 and 53 of the '653 patent). Prometheus discovered a correlation between metabolite levels in a patient's blood and therapeutic efficiency. It then invented a method to optimize therapeutic efficiency while minimizing side effects by determining metabolite levels and identifying a need to adjust drug dosage upward or downward based on the levels.

86. The Federal Circuit applied its recently

articulated *Bilski* "machine-or-transformation" test and held that Prometheus's claimed methods satisfied the transformation prong of the test and reversed the district court's summary judgment grant of invalidity. *Id.* at 1343-48, 1350. The Court did not address the machine prong.

87. Most relevant to this case, the court held that the claimed "determining the level of 6-thioguanine" in a patient was transformative because "[s]ome form of manipulation . . . or other modification of the substances to be measured, is necessary to extract the metabolites from a bodily sample and determine their concentration." *Id.* at 1347.

88. The Federal Circuit quoted approvingly Prometheus's expert: "'at the end of the process, the human blood sample is no longer human blood; human tissue is no longer human tissue.'" *Id.*

89. The Federal Circuit rejected Mayo's argument that such manipulation of the sample was "merely a necessary data-gathering step" and instead found that transforming the sample was "central to the purpose of the claims." *Id.* "Measuring" the metabolite levels was what enabled possible adjustments to the drug dosage to optimize efficacy or reduce toxicity. *Id.*

90. Similarly in this case, Myriad's method claims each requires the transformation of a tissue or blood sample in order to isolate the patient's DNA and thus would satisfy the *Bilski* transformation test. Further, Myriad's manipulation of the sample is "central to the purpose of the claims," just as it was to Prometheus's method. Transforming the tissue or blood sample is what enables making the comparison

between the wild-type gene and the patient's gene and therefore the detection of any germline alteration.

91. In addition to the transformation of the human sample, the Myriad method claims require further manipulation of the isolated DNA fragment to perform the detecting step. For example, hybridization can be used to bind the isolated DNA in single strand format, thereby transforming the single stranded DNA into a new molecule called a "hybridization product." *See, e.g.*, claim 5 of the '999 patent ("a germline alteration is detected by hybridizing a BRCA1 gene probe . . . to genomic DNA isolated from said sample and detecting the presence of a hybridization product").

92. Other dependent claims in each of the method patents reflect a number of manipulations of the isolated DNA encompassed by the terms "detecting," "screening," "identifying" and "diagnosing" and envisioned by the inventors. Each of these manipulations involves a transformation of isolated DNA fragment into a different, non-naturally occurring form.

93. In *Prometheus*, the Federal Circuit distinguished *In re Grams*, 888 F.2d 835 (Fed. Cir. 1989) because "the essence of the claimed process" in *Grams* was a mathematical algorithm. 581 F.3d at 1348. The court in *Prometheus* observed: "The patent and thus the court focused only on the algorithm rather than the clinical tests purported to be covered by the claims." *Id.*

94. Significantly in *Grams*, the court posed the "critical" question: "What did applicants invent?"

888 F.2d at 839. The answer in *Grams* was a mathematical algorithm, since performing the clinical tests was already in the prior art and not the focus of the specification. *Id.* at 839.

95. This case elicits a very different answer to the critical question, what did applicants invent? Myriad's invention is not a mathematical algorithm but instead is a novel diagnostic procedure based on their discovery of a correlation between mutations in the *BRCA*1 and *BRCA*2 genes and certain cancers. Thus, unlike the situation in *Grams*, the transformative steps of collecting and analyzing tissue and blood samples for the BRCA1 relevant mutations must be treated as central to the claimed invention. *See* ¶ 93 above.

96. Further, Myriad's claims are not analogous to those in *Gottschalk v. Benson*, 409 U.S. 63 (1972), or *Parker v. Flook*, 437 U.S. 584 (1978), based on similar reasoning. Each of these cases, like *Grams*, involved an attempt to patent a mathematical formula or algorithm, as part of a software program, in the absence of an inventive application.

97. Significantly, Myriad's method claims do not involve a mathematical algorithm as that term was used in *Benson* and *Flook* or a software program for performing a mathematical algorithm. Neither do they involve pure information. Rather, they involve chemical molecules that are capable of many complex reactions yet to be fully understood, including replication, transcription and translation. The fact these molecules are abbreviated with the first letters of their nucleotides does not make the abbreviated recitation purely information. *See supra* ¶ 45.

98. Even if *Benson* and *Flook* are relevant here, they are easily distinguished. Benson's claimed invention was to "a method of programming a general purpose digital computer to convert signals from binary-coded decimal form into pure binary form." 409 U.S. at 66. No new machinery was necessary and, in fact, the algorithm could be performed without a computer. *Id.* at 68. The Court concluded the claims were to the algorithm itself and thus not patentable. *Id.* at 72-73.

99. In *Benson*, the Supreme Court recognized a process could be patentable without requiring a machine: "'That a process may be patentable irrespective of the particular form of the instrumentalities used cannot be disputed. . . . A process is a mode of treatment of certain materials to produce a given result. It is an act, or a series of acts, performed upon the subject matter to be transformed and reduced to a different state or thing.'" *Benson*, 409 U.S. at 69-70 (quoting *Cochrane v. Deener*, 94 U.S. 780, 786-87 (1876)) (a case involving a process for manufacturing flour to improve its quality)).

100. Immediately following its discussion of *Cochrane*, the Supreme Court reiterated: "Transformation and reduction of an article 'to a different state or thing' is the clue to the patentability of a process claim that does not include particular machines." *Id.* at 70. This test has become known as the "machine-or-transformation test" presently being considered by the Supreme Court in *Bilski v. Kappos*, 129 S. Ct. 2735 (2009)

(argued Nov. 9 (2009)) and applied by the Federal Circuit in *Prometheus*. *See supra* at ¶¶ 85-90.

101. Again, Myriad's method claims involve several transformative manipulations of tissue or blood and the DNA to detect a genetic mutation in the *BRCA*1 or *BRCA*2 gene. Thus. the method claims involve "an act, or series of acts, performed upon the subject matter to be transformed and reduced to a different state or thing," and therefore are to statutory subject matter under *Benson*.

102. In *Parker v. Flook*, the claimed invention involved a computer program for determining when an alarm limit was reached. 437 U.S. at 585 (1978). Like the situation in *Benson*, in *Flook*, the only novel feature of the claimed method was a mathematical algorithm. *Id.* at 585-86. The Court concluded: "Respondent's process is unpatentable under § 101, not because it contains a mathematical algorithm as one component, but because once that algorithm is assumed to be within the prior art, the application, considered as a whole, contains no patentable invention." *Id.* at 594.

103. In contrast, Myriad's claimed methods are not based on a mathematical algorithm but rather on the application of their discovery that a particular DNA sequence is associated with certain cancers to provide a diagnostic tool for such cancers. Further, even assuming the newly discovered correlation is analogous to a mathematical algorithm, the practical application of that correlation is entitled to patent protection under the *Benson* and *Flook* analyses.

104. This case is more analogous to *Diamond v. Diehr*, 450 U.S. 175 (1981) than it is to *Benson* or

Flook. The claimed subject matter in *Diehr* was a process for curing rubber which included a mathematical algorithm and a programmed digital computer. *Id.* at 178. Respondents did not seek a patent on a mathematical algorithm but rather on a process for curing rubber. *Id.* at 188. Recognizing that "an *application* of a law of nature or mathematical algorithm to a known structure or process may well be deserving of patent protection," *id.* (emphasis in original), the Court held Diehr's claims eligible for patenting. *Id.* at 193-94.

105. Similarly, Myriad's method claims are to an application of a law of nature—a method for detecting a germline alteration linked to breast and ovarian cancer—and not to the law of nature itself.

106. Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct.

/s/ Nancy J. Linck
Nancy J. Linck

Executed on: Dec. 23, 2009

EXHIBITS 1-3

[EXHIBITS 1-3 OMITTED]

[Supplemental Declaration of Ellen T. Matloff, filed January 20, 2010] [Caption Omitted In Printing]

1. My name is Ellen T. Matloff. I am the Director of the Cancer Genetic Counseling Shared Resource at the Yale Cancer Center in New Haven, Connecticut. I am also a Research Scientist in the Department of Genetics at the Yale University School of Medicine.

2. I am a plaintiff in this case. The statements herein represent my views as an individual and not those of Yale University.

3. I previously submitted a declaration in support of Plaintiffs' Motion for Summary Judgment. Matloff decl., Aug. 12, 2009.

4. I am informed that the declaration of Gregory C. Critchfield, defendant Myriad's President, submitted in connection with Myriad's opposition to plaintiffs' motion for Summary Judgment discusses the number of scholarly articles that have been written concerning BRCA1/2. I am informed that, as one example, he refers to 17 papers I have written on BRCA1/2. Critchfield ¶ 4, Exh. 4.

5. My *curriculum vitae* was attached to my prior declaration. An examination of the papers listed in that *vitae* reveals that the vast majority of the papers I have written on BRCA1/2 are observational based on our experience in counseling patients who have tested positive for mutations on the BRCA1/2 genes. For example, I wrote a paper on sexuality of women who had their ovaries removed at an early age, in part as a result of receiving a positive BRCA 1/2 result. Matloff ET, Bober S, Barnett RE. Unraveling the Next Chapter: Sexual Development, Body Image

and Sexual Functioning in Female BRCA Carriers. *The Cancer Journal* 2009; 15(1):15-18. Research and writing of this kind does not require me to take any action to infringe Myriad's patent.

6. I would like to research, write, and publish other papers but I have not done so because I cannot do so without infringing Myriad's patents. For example, I would like to research protein truncation testing and other alternative screening methods to identify mutations in BRCA Carriers. I would like to research the percentage of patients with (triple-negative breast cancers, medullary breast cancers, breast cancers with medullary features, isolated breast cancers between ages 40-50, male breast cancer, epithelial ovarian cancer pancreatic cancer) who carry a BRCA mutation on full sequencing. I would like to research the percentage of patients with (same options as above) who carry a BRCA mutation found on large rearrangement and deletion testing. I would like to research the percentage of patients who tested BRCA negative before Myriad Genetics began offering BART testing who actually carry a BRCA mutation using large rearrangement and deletion testing. I would like to research chemopreventive medications (in the SERM category, such as tamoxifen) specifically geared toward female BRCA carriers which reduce the risk of both breast and ovarian cancers.

7. In order to do these types of research, I would have to do actions that I believe would legally infringe on Myriad's patents. I understand Myriad now asserts that it would never enforce its legal right to sue me for those actions if I were doing them for purely research purposes. Myriad has never told me

that and I am unaware of any written statement by Myriad (at least until their submissions in this case) giving me such permission. I am extremely reluctant to engage in behavior that could subject me to a successful suit for infringement based on the hope that Myriad will exercise its discretion not to sue me particularly because I was told by Myriad that we could not even offer our highest risk patients testing for large rearrangements and deletions, which they needed clinically, before their BART testing was available.

8. Thus, whatever the level of research that has occurred with respect to BRCA1/2, I am confident that more would have occurred if the patents did not present a legal impediment.

9. I am informed that Dr. Critchfield also refers to the role played by the Yale DNA Diagnostic Laboratories in affording women "testing for specific BRCA mutations." Critchfield at ¶ 62. He is correct that the Yale DNA Diagnostic Laboratories offer "testing for specific mutations." http://info.med.yale.edu/genetics/DNA/BRCA-ASH.html; http://info.med.yale.edu/genetics/DNA/BRCA-Familial.html.

11. However, his observation is misleading. The testing offered by Yale is very limited. Yale and other labs can confirm positive test results if the familial mutation is identified by Myriad. However, if a person has full sequencing via Myriad and tests negative (this encompasses the vast majority of all test kits ordered through Myriad), that person cannot have a second opinion by ordering full sequencing elsewhere. That would be an

infringement of the patent and Yale's licensing agreement with Myriad does not permit it.

I declare, pursuant to 28 U.S.C. §1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Ellen T. Matloff

Ellen T. Matloff, MS

Executed on January 5, 1020 (sic)

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[Declaration of Thomas Kepler, filed January 20, 2010] [Caption Omitted In Printing] [Exhibit 1 Omitted]

1. I am a Professor in the department of Biostatistics and Bioinformatics at Duke University Medical Center. My research includes the computational analysis of genes and genomes, as well as other topics in computational biology. A copy of my current *curriculum vitae* is attached.

2. My co-authors and I wrote a paper on Claim 5 of the '282 patent, translating its form into a computational algorithm that was also empirically tested against DNA sequence data. That paper is attached as Exhibit 2. It has been submitted for publication. Our method of analysis is widely recognized by experts in the fields of bioinformatics, computational biology, genetics, and genome sciences. Our conclusions are fully supported by the data.

3. My co-author, Robert Cook-Deegan, circulated copies of the paper to counsel for all of the parties in this case on December 22, 2009.

I declare pursuant to 28 U.S.C. §1746, under penalty of perjury under the laws of the United States that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Thomas Kepler

Thomas B. Kepler

Executed this 6th day of January, 2010

EXHIBIT 1

[EXHIBIT 1 OMITTED]

EXHIBIT 2

"Metastasizing patent claims on BRCA1"

Thomas B. Kepler[1], Colin Crossman[2], Robert Cook-Deegan[3]

[1] Department of Biostatistics and Bioinformatics, Duke University. Durham NC 27705

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[3] Institute for Genome Science and Policy and Sanford Institute, Duke University, Durham NC 27705

In 1998, the US Patent and Trademark Office granted Mark H. Skolnick and ten of his collaborators a patent on the human gene BRCA1 (US Patent 5,747,282). Mutations in BRCA1 confer a substantial risk for breast and ovarian cancers, with a cumulative risk of incidence by age 70 of 69% (breast) and 39% (ovarian) (1). Genetic tests to screen for these mutations in the United States are available exclusively through Myriad Genetics, an assignee of the patent. Women with a family history of breast and ovarian cancer may, through this genetic test, determine whether they carry one of the high-risk alleles, and if so, decide whether to take prophylactic action, generally surgical removal of breasts, ovaries or both.

Human gene patents are controversial (2); *BRCA1* patents are currently the subject of litigation (3). This particular patent is the first one named in a complaint filed by the American Civil Liberties Union and is now moving swiftly toward resolution. A hearing in the Southern district federal court of New York took place September 30, 2009, before Judge Robert W. Sweet (4). On November 2, he released an 88-page decision to continue the case (5).

The patent itself is complex and makes several different claims. One of these claims seemed to us particularly broad, so we investigated it, doing simple calculations to estimate its reach, and testing our findings by direct analysis of the extent of its reach within parts of the human genome. We find that, through this claim, the patent extends to portions of most genes in the human genome and likely to most genes in nature as well.

The patent first makes claim 1, to "An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2." SEQ ID NO:2 is the 1863-residue amino acid sequence for the protein encoded by the BRCA1 gene. The patent further claims "5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1." Note that the claim in one is for DNA coding for the polypeptide, not for any specific gene. There are, of course, many polynucleotides that would encode the BRCA1 polypeptide. Claim 5, then, is a claim on any 15-mer oligonucleotide found in any such sequence. We estimate that the human genome contains over one million oligonucleotides covered by this claim, and that most human genes contain at least one and usually several oligonucleotides covered by the claim.

To estimate the breadth of this claim, one can perform a short computation. Accounting for bias in the usage of amino acids as reported, for example, in (6), the usage-weighted geometric mean codon degeneracy per amino acid is 3.107. Therefore, the mean number of 15-mers encoding a polypeptide of length 5 chosen at random from a vertebrate proteome is 3.107^5, about 290. There are 5,575 15-

mers in BRCA1, so, if we consider all of the nucleotide sequences that encode the BCRA1 protein, there are about 1.6×10^6 15-mers embodied by the claim. There are $4^{15} = 1.07\times 10^9$ different 15-mers altogether, so the probability that a 15-mer chosen at random will be covered by the claim is $p = 1.6\times 10^6 / 1.07\times 10^9 = 0.0015$. A typical human gene (before RNA editing) contains 10,000 bases, so, if human genes were random strings of nucleotides, one would expect a human gene to contain an average of 15 15-mers claimed under the patent.

But human genes are not random strings, so we counted the number of claimed 15-mers in a representative sample of the human genome to test the breadth of claim 5 empirically. We examined chromosome 1 (NCBI build 37. 1), and counted only a subset of claimed 15-mers. The reason for counting only a subset is that there are three amino acids (serine, leucine, and arginine) that have 6-fold degeneracy. If we neglect two of the six synonymous codons for each of these amino acids, each degenerate 15-mer can be represented as a single string of 15 letters, with degenerate positions encoded by the extended IUPAC nucleotide alphabet. This representation permits a many-fold reduction in computing time that will slightly understate the degree of redundancy and breadth of claim 5.

Examining only this subset, we find over 340,000 matches of claimed 15-mers to the 250 million base pairs of chromosome 1, for an empirical hit rate of $p_{emp} = 0.00136$ per 15-mer, close to our theoretical expectation. Using this conservative estimate, we expect about 14 infringing sequences per human gene. The claims being discussed are structural, and do not restrict acts of infringement to particular uses or contexts, but should, in theory, give the patent-holders exclusive rights to make, use, sell, or import the claimed 15-mers in the United States, including use in research, diagnosis or other domains. These claims are not, for example, restricted to sequences actually derived from a BRCA1 sequence, or from human chromosome 17 (where BRCA1 is located), or only those 15-mers that are unique to BRCA1, or for use only in the context of risk assessment, diagnosis, treatment or research on inherited risk of breast and ovarian cancer. That is, anyone making an "isolated" DNA that includes any one of the 15 base-pair sequences in the United States for any purpose would be infringing US patent 5,747,282.

To test the practical significance of claim 5, we examined the 713 entries in GenBank that represent complete coding sequences for human mRNAs deposited in 1994 (the year before the patent application was filed); 568 of these 713 mRNAs (79 percent) contain at least one BRCA1-derived 15-mer using the restricted codon table. Note that these mRNA sequences are shorter than typical genes, with a median length of 1902 nucleotides.

These findings suggest that there were already many sequences in GenBank covered by claim 5 at the time the patent application was filed.

The particular strategy for claiming DNA sequences exemplified by claim 5 is quite broad. The patent examination manual stipulates that claims use "the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification (7)." Lines 14-4 of. column 24 in the patent define "substantial homology or similarity" as "nucleotide sequence identity in at least about 60% of the nucleotide bases," and defines "selective hybridization" "when there is at least about 55% homology over a stretch of at least about 14 nucleotides." These definitions explain why 15-mers were chosen, but do not alter the plain meaning of any of the terms in claim 5. Our experimental sequence comparisons also meet these definitions.

Once granted, patent claims are valid until and unless they are challenged. BRCA patents were cited in enforcement letters that Myriad Genetics sent to other laboratories to cease genetic testing for BRCA mutations (8,9).

It is worth noting that a 1991 patent application for Expressed Sequence Tags was rejected on several grounds, including the fact that claimed 15-mer oligonucleotides were found in existing DNA sequences. This finding that 15-mers had sequence identity to many genes was published, and so publicly known by the end of 1992 (10). That particular patent application was abandoned by NIH in 1994. Examiner James Martinell estimated that to examine the reach of the oligonucleotide claims in that patent would have taken until 2035 because of the computational time required to search for matches in over 700,000 15-mers claimed, roughly half the number granted in claim 5 of US Patent 5,747,282. Although still computationally intensive, such sequence comparisons can clearly can be done much more rapidly now. The reason this was not done by a different examiner for US Patent 5,747,282 when it was being examined between 1995 and 1998 is not clear.

The judgment in this case is likely to have impact on the practice of biomedicine and the pursuit of research. The enormously improved capability to examine the reach of partially ambiguous claims should provide important guidance along the way.

1. Antoniou A, Pharoah PDP, Narod S, Risch HA, Eyfjord JE, et al. (2003) Average Risks of Breast and Ovarian Cancer Associated with BRCA1 or BRCA2 Mutations Detected in Case Series Unselected for Family History: A Combined Analysis of 22 Studies. Am J Hum Gen 72: 1117- 1130.

2. Paradise J, Andrews L, Holbrook T (2005) INTELLECTUAL PROPERTY: Patents on Human Genes: An Analysis of Scope and Claims. Science 307: 1566-1567.

3. *Association for Molecular Pathology, et al., v. United States Patent and Trademark Office, et al.*, No. 09-CV-4515 (RWS) (S.D.N.Y. filed May 12, 2009) (plaintiffs' complaint).

4. *Association for Molecular Pathology, et al., v. United States Patent and Trademark Office, et al.*, No. 09-CV-4515 (RWS) (S.D.N.Y. August 27, 2009) (order setting date for hearing of plaintiffs' motion for summary judgment and jurisdictional discovery).

5. *Association for Molecular Pathology, et al., v. United States Patent and Trademark Office, et al.*, No. 09-CV-4515 (RWS) (S.D.N.Y. November 2, 2009) (opinion stating the suit will continue, keeping all defendants and setting dates for motions and for a December 11, 2009, oral hearing).

6. King JL, Jukes TH (1969) Non-Darwinian Evolution. Science 164: 788-798.

7. US Patent and Trademark Office, *Manual of Patent Examining Procedure*, Section 2111.

8. R. Cook-Deegan *et al.*, *Impact of Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers to Colon Cancers* (Case study commissioned by the Secretary's Advisory Committee on Genetics, Health, and Society, 2009; http://oba.od.nih.gov/oba/SACGHS/Appendix%201%20SACGHS%20Patents%20Consultation%20Draft%20Compendium%20of%20Case%20Studies.pdf).

9. E. R. Gold, J. Carbone, *Myriad Genetics: In the Eye of the Policy Storm* (International Expert Group on Biotechnology, Innovation and Intellectual Property, 2008; http://www.theinnovationpartnership.org/data/ieg/documents/cases/TIP_Myriad_Report.pdf)

[Declaration of Robert L. Nussbaum, filed January 20, 2010] [Caption Omitted In Printing] [Exhibit 1, 2 Omitted]

I, Robert L. Nussbaum, declare under penalty of perjury that the following is true and correct:

1. I offer my opinion herein on the science of genetics and the biology of DNA, including methods for its extraction and isolation. My opinion is based on the facts or data cited in this declaration, and on my own original research. A true and correct copy of my Curriculum Vitae is attached hereto as an Exhibit.

2. My qualifications as an expert are as follows. I received my A.B. *cum laude* in Applied Mathematics from Harvard College in 1971. I received my M.D. Medicine from Harvard Medical School in 1975.

3. I currently serve at the University of California, San Francisco (UCSF) as a tenured Professor of Medicine In Residence, as a Professor of Neurology (Joint Appointment), and as the Holly Smith Distinguished Professor of Science and Medicine. I am Chief of the Division of Medical Genetics in the UCSF Department of Medicine, and Executive Committee Member of the UCSF Institute for Human Genetics. Since 2006, I have served as Consultant in Genetics at UCSF Medical Center as well as Faculty in the Biomedical Sciences Graduate Group at UCSF. Since 2008 I have been the Director of the Cancer Risk Program of the Diller Family Comprehensive Cancer Center at UCSF, which provides clinical care and genetic counseling for families with hereditary cancer syndromes and the

Director of the Program in Cardiovascular Genetics of the Heart and Vascular Center of the UCSF Medical Center.

4. Prior to my current appointments at UCSF, I was Assistant Professor of Medicine at Baylor College of Medicine from 1981 to 1984. Later, at the University of Pennsylvania School of Medicine (Primary), I was Assistant Professor of Human Genetics from 1984 to 1989, Associate Professor of Human Genetics from 1989 to 1993, and Professor of Genetics from 1993-1994, as well as an Associate Investigator of the Howard Hughes Medical Institute. From 1994 to 2006 I was a Principal Investigator and Chief of the Genetic Disease Research Branch in the Intramural Research Program of the National Human Genome Research Institute.

5. I have been invited to give lectures and present papers at various genetics conferences, including "Genomics in Social and Behavioral Research" in September 2008 at the NHGRI, Bethesda, MD; "Molecular Genetic Approach to Parkinson Disease" in April 2008 at the Gallo Institute, Emeryville, CA; "What Human Genetics has taught us about Alzheimer Disease" in June 2007 at the Alzheimer's Association Medical Scientific Advisory Council Research Symposium, Stanford University; "Genetic Testing" in November 2006 at the President's Council on Bioethics; and "Direct to Consumer Genetic testing" in September 2006 at the National Genetic Policy Summit, Washington, D.C. In 2004, I was elected to the Institute of Medicine of the National Academy of Sciences.

6. My recent publications include "Genomics and the Human Genome Project" in The Molecular and Genetic Basis of Neurological and Psychiatric Disease, 4th edition (eds R. Rosenberg, S. Prusiner, S. DiMauro, R. Barchi, E. Nestler), Butterworth Heinemann, Woburn, MA, 2007; "Genetics of disease: Recent advances in the genetics of human disease offer something new for every scientific interest". Curr. Opin. Genet. Develop. 17:1-3, 2007; and "2004 Presidential Address: What is so Special about the 'Human' in 'Human Genetics', Amer. J. Hum. Genet. 76(2):198-202, 2005. I am also the lead author on the previous (6th) and most recent (7th) edition of a widely used medical genetics textbook entitled "Genetics in Medicine", published in 2007.

7. In addition to my academic practice, I also have a clinical practice and see children and adults for the diagnosis, management and counseling of hereditary diseases, including Hereditary Breast and Ovarian cancers caused by mutations in *BRCA1* and *BRCA2*. I am currently certified by three Specialty Boards: the American Board of Internal Medicine, the American Board of Medical Genetics in Clinical Genetics, and the American Board of Medical Genetics in Clinical Molecular Genetics. From 1984 to 1993, I was Physician in the Division of Human Genetics at Children's Hospital of Philadelphia. From 1994 to 2006, I was Clinical Staff at the National Institute of Health (NIH) Clinical Center. At UCSF, I currently spend approximately 80% of my time on academic work and 20% of my time on clinical work.

8. I have also engaged in government service with respect to the field of human genetics. For

example, I have served the National Center for Human Genome Research Institute (NHGRI) in various roles since 1989 to the present. In 2001, I chaired the Subgroup on Genotyping Methods for the SNP Mapping Advisory Committee at NHGRI. From 1995 to 2006, I was Acting Chief of the Inherited Disease Research Branch at NHGRI. From 1996 to 2006, I also was the lead Project Officer for the Center for Inherited Disease Research, an inter-Institute genotyping facility that provides up-to-date genetic analysis to NIH-funded researchers around the United States.

9. At NIH, I was a regular member of three Initial Review Groups: the Genetic Basis of Disease, NIGMS (1987-1991), the Human Genome Research Study Section (DRG) (1992-1996), and Mammalian Genetics (CSR) (1998-2000), as well as serving on numerous ad hoc Review Panels.

10. I taught human genetics for Medical Students at the University of Pennsylvania from 1986 until 1996 and was Course Director from 1997-2003. I also taught human genetics at National Human Genome Research Institute from 1999 to 2006, including the courses "Introduction to Human Genetics for Genetic Counseling Students" and "Introduction to Clinical Molecular Genetics." I currently teach genetics to medical students and graduate students at UCSF and to genetic counseling students at the California State University, Stanislaus.

11. I have reviewed the Declaration of Dr. Mark A. Kay and the Defendants' Memorandum of Law (1) in support of their motion for summary judgment and

(2) in opposition to plaintiffs' motion for summary judgment. In this declaration, I explain how the definition of "isolated DNA" in Defendants' patents covers both naturally-occurring DNA and synthetic DNA, and how the DNA that has been patented is not structurally and functionally different from genes in nature.

DEFINITION OF "ISOLATED" DNA AND THE PROCESS OF ISOLATION

12. When the Defendants argue that an isolated segment of genomic DNA is a man-made substance that is substantially different from the DNA that constitutes a native gene inside a cell, they blur the distinction between three entities: "DNA", "chromatin" and "gene". Their patent defines "isolated DNA" as follows:

> An "isolated" or "substantially pure" nucleic acid (*e.g.*, an RNA, DNA or a mixed polymer) is one which is substantially separated from other cellular components which naturally accompany a native human sequence or protein, *e.g.*, ribosomes, polymerases, many other human genome sequences and proteins. The term embraces a nucleic acid sequence or protein which has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems. '473 Patent, col.

19:6-15; '282 Patent, col. 19:8-18; and '492 Patent, col. 17:62 – col. 18:5.

(I must point out that such a broad claim that the term "'isolated' or 'substantially pure'" nucleic acid "embraces... a protein" is an impossibility since protein is not a nucleic acid.)

13. Although this definition of "isolated" equates the terms "isolated" and "substantially pure" with reference to nucleic acids, "isolated" nucleic acid and "substantially pure" nucleic acid do not mean the same thing. In addition, this definition blurs the distinction between DNA isolated from the cell and synthetic DNA, such as primers made using chemical reactions or biochemical procedures.

14. I would like to clarify that some of the "isolated DNA" covered by the patent claim -- a DNA segment of interest from a natural source (as opposed to synthetic DNA) – results from a process that occurs in two steps: (1) extracting the DNA away from other non-DNA substances including the proteins that make up the "chromatin" in which DNA is packaged, and (2) separating the segment of human DNA with the sequence of interest away from the rest of the genomic DNA. These two steps are functionally distinct.

15. When DNA is obtained from a natural source, extraction of cellular DNA is a routine biochemical procedure in which all the DNA in a sample of cells or tissue is separated away from other non-DNA substances including the proteins that make up the "chromatin" in which DNA is packaged. Extraction is a chemical process that takes advantage of the chemical properties of DNA (such as its solubility in

various liquids) and does not discriminate between one segment of DNA containing a sequence of interest from other segments containing other sequences. With extraction, there is no separation of a particular DNA segment of interest away from the rest of cellular DNA.

16. Separating a DNA segment containing a sequence of interest away from the rest of the DNA relies on the sequence. Although separation may be accomplished by biochemical methods, such as excising that segment or amplifying it by PCR, it is also possible to use biological methods to separate the DNA containing a gene away from other genes without extracting it. Random pieces of DNA can be transferred into non-human cells or microorganisms and the subset of the cells or microorganisms that have acquired a novel property as a result of having taken up the segment of interest containing specific information encoded in the DNA sequence within that segment can be identified and isolated as pure colonies. In this way, the DNA segment containing a sequence of interest of human DNA in an individual colony of bacteria or cells is in fact separated away from all the other human DNA of the original cell from which the DNA had been obtained, even though it has not been extracted away from bacterial proteins or separated from bacterial DNA.

"ISOLATED" DNA IS NOT MAN-MADE OR STRUCTURALLY DISTINCT FROM DNA IN ITS NATURAL STATE IN THE CELL

17. Isolating a DNA segment of interest therefore depends on extraction of cellular DNA and separation of the DNA segment of interest

away from other genomic DNA. This distinction is important when assessing the validity of the claim Dr. Kay makes in paragraph 137 of his declaration:

> "The isolated DNAs are excised, extracted or synthetic chemical compounds made by the hands of molecular biologist, not by nature. They are structurally distinct from any substance found in the human body—indeed, in all of nature."

18. To the contrary, I would argue that isolated DNA is not made by the hands of a molecular biologist, but is instead simply extracted from the chromatin. Moreover, when isolating a DNA segment of interest, neither extracting total cellular DNA nor separating a particular DNA segment away from the rest of DNA produces a substance that is "structurally distinct from any substance found in the human body". Instead, an isolated DNA segment, as DNA, is not significantly different from the same segment of DNA in the cellular DNA from which it was derived.

19. With regards to the extraction step, Dr. Kay has confused chromatin and DNA. The structural difference he points to between DNA in a cell and DNA isolated from a cell are actually differences between chromatin and DNA, not between the DNA in a cell and the DNA isolated from a cell.

20. Any differences between isolated DNA and DNA in chromatin are actually "epigenetic" changes (note, they are not "genetic"), which means they are superimposed upon genes and not part of a gene

itself. The one epigenetic modification of DNA that is not part of chromatin, the modification of DNA by the covalent attachment of methyl groups to the cytosine ring, is preserved in genomic DNA after it is extracted and so does not distinguish the DNA in a cell from the DNA extracted from a cell.

21. DNA swathed in proteins as a component of chromatin inside a cell is not structurally different from DNA after it has been extracted away from other cellular substances, including chromatin. By analogy, the element gold is still gold whether it is a streak of metal embedded in low grade ore or is a nugget that has been extracted away from the silicates in which it is embedded. Thus, with regards to the extraction step required to do what the Defendants claim is to "isolate" a segment of DNA from natural sources, I reject the argument that this "isolated" DNA is "structurally different" from natural DNA.

22. With regards to the separation step, once total DNA has been extracted from a cell, the isolation of any particular segment of interest occurs on the basis of the particular sequence of DNA bases it contains. It is the DNA sequence that distinguishes the segment being isolated from all the other segments of genomic DNA from which it is being separated. Fundamentally, then, a segment of extracted DNA can be separated from the rest of the genomic DNA because it contains genetic information of interest, e.g. it contains the information that comprises a gene. The very same sequence of bases in the DNA that allows scientists to distinguish one segment of extracted DNA and makes that segment of interest is

also contained in the DNA when it is in its natural state in the cell.

23. Therefore, with regards to the isolation of a DNA segment of interest from natural sources, such as a cell, the claim that "isolated DNAs...are structurally distinct from any substance found in the human body—indeed, in all of nature" is incorrect on two grounds. First, in extracting cellular DNA, the structural distinction claimed by Dr. Kay is between chromatin and DNA, not between extracted DNA and cellular DNA. Second, isolating a segment of DNA of interest by separating it from the rest of the extracted genomic DNA depends on the sequence of DNA bases that is present in both the isolated segment and the natural segment in the cell. Thus, "isolated DNA", meaning DNA that has been extracted away from other cellular components and then separated from the rest of the DNA in the cell, is not made by the hand of the scientist; it is extracted away from chromatin and then separated from the rest of the genomic DNA based on its sequence of bases and/or the information the bases contain. A segment of isolated DNA is no more a product of the hand of man than is the gold that has been extracted from other minerals based on its natural, and not man-made, physical and chemical characteristics.

AN "ISOLATED" GENE IS NOT STRUCTURALLY AND FUNCTIONALLY DISTINCT FROM GENES IN NATURE

24. "Gene" is a term that came into use long before it was known what genes were made of. A gene was defined as a unit of heredity that carries

the information necessary to pass whatever trait or function the gene is responsible for from one generation to the next. Thus, I agree with Dr. Kay's heredity-based definition of a gene in paragraph 142 of his declaration, where he states:

> "Historically, the term "gene" has been used to describe the unit that is responsible for the inheritance of a discrete trait, such as the color of peas in a peapod."

25. Although Dr. Kay uses the term "historically", this definition is still as valid as any other up to the present day. With progress in molecular genetics, however, genes can now also be defined in molecular terms. Dr. Kay writes in paragraph 143 of his Declaration:

> "In molecular terms, a gene is an aggregate of *several segments of a chromosome* (emphasis added). Some segments regulate the activity of the gene. From other segments, various types of RNA are produced".

This molecular definition of a gene is ambiguous. When speaking of "several segments of a chromosome", does Dr. Kay mean that a gene is an aggregate of several segments of the DNA in a chromosome, some of which regulate the activity of the gene, such as promoter or enhancer elements within the DNA, and others which contain the triplet code? Or, is he saying a gene is an aggregate of several segments of the chromatin that make up a chromosome and that a gene also includes the epigenetic modifications, such as methylation or proteins that are involved in regulating the gene? Furthermore, when a gene is regulated by a protein such as a transcription factor or a regulatory non-coding RNA encoded by a separate, distinct gene on that chromosome, Dr. Kay's definition would then include the DNA sequence of that second gene as part of the first gene, thereby converting two distinct genes into one. Dr. Kay goes on in paragraph 173 to draw a major distinction between isolated DNAs and the naturally occurring genes in the cell.

> "Isolated DNAs are structurally and functionally distinct from any DNA found in nature. The isolated *BRCA1* and *BRCA2* DNA molecules claimed in the *BRCA1* and *BRCA2* patents are likewise extracted, purified, or synthetic, and are structurally distinct from any substance found in the human body, or elsewhere in nature. For example, native DNAs are physically connected to DNA regulatory sequences and proteins that determine which DNA sequences are expressed, how and where they expressed, and their level of expression. In contrast, the claimed isolated *BRCA1* and *BRCA2* DNAs are not associated with these regulators and do not contain this information."

26. Taking the definition of a gene as a unit of heredity that carries the information necessary to pass a trait or function from one generation to the next, the correct view is that a gene such as *BRCA1* or *BRCA2* is composed of a segment of DNA in a

chromosome and *not* the chromatin or other regulatory proteins.

27. In claiming a patent on isolated DNA sequences that contain the information that comprises the *BRCA1* or *BRCA2* gene, the Defendants have attempted to patent a naturally occurring entity, a gene, basing their claim on alleged and, at best, highly irrelevant differences between the naturally occurring gene and the isolated DNA sequences. That this is the correct interpretation of the coverage of their patent claim is supported by a number of important biological facts, explained as follows.

28. During reproduction, DNA is unpackaged, stripped of chromatin proteins and other epigenetic modification such as some or all of the cytosine methylation, partially or substantially remethylated and repackaged into chromatin as it is passed through the germ line from one generation to the next. Although these modifications are more striking in the production of sperm compared to ova, they occur in both parents. Most importantly, they make clear that it is indeed the DNA that constitutes a gene because the proteins and other epigenetic modifications that surround DNA in chromatin are substantially changed every generation while it is the DNA that remains constant (save for rare spontaneous mutation) and is responsible for passing along the genetic information.

29. With the one notable exception of genomic imprinting, it is DNA -- and *only* DNA, and the information in it -- that is responsible for the transmission of traits from one generation to the next and, therefore, constitutes the genes. Since

neither *BRCA1* nor *BRCA2* has been shown to undergo imprinting, the *BRCA1* and *BRCA2* genes are also wholly contained in the DNA, whether in chromatin or in an isolated state without epigenetic modification. The DNA containing the *BRCA1* or *BRCA2* genes are responsible for how a trait determined by either the *BRCA1* and *BRCA2* genes is passed on from one generation to the next.

30. Second, there are cell culture experiments that show that genomic DNA can transmit a trait, regardless of whether it is isolated or present inside the cell in chromatin. There are two classic experiments, one published 65 years ago, the other 27 years ago, that prove that DNA is the essence of genes.

31. In the first experiment, isolated DNA was shown to contain all the genetic information necessary to change a non-pathogenic living bacterial organism into a pathogenic bacterium. Certain strains of the bacteria *Streptococcus pneumoniae* are distinguished by whether the surface of their cell wall, the capsule, is "smooth" or "rough" when observed under the microscope. These two different cell walls correlate with how disease-producing the bacteria are: the smooth bacteria cause rapid death when injected into mice, bacteria with the rough capsule do not. In 1944, Avery, MacLeod and McCarty reported that DNA extracted from a sample of a killed pathogenic smooth strain of the bacteria *S. pneumoniae* was able to change a rough non-pathogenic strain into a smooth pathogenic strain by the process known as transformation, the introduction of DNA or RNA into a cell (Avery OT, MacLoed CM and McCarty M Studies on the

Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types, J. Exp. Med. 79:137, 1944). DNA from a sample of killed pathogenic smooth *S. pneumoniae* was extracted away from the non-DNA substances of the bacteria to a level of purity of 99.98%. The extracted DNA was dissolved in growth medium into which a non-pathogenic strain of *S. pneumoniae* were inoculated and grown. In these cultures, live smooth, pathogenic bacteria appeared because they were "transformed" by the extracted DNA. These originally rough bacteria were permanently changed to smooth and passed on their smooth character to all subsequent offspring. Thus, all the genetic information necessary to change the genes of a non-pathogenic living bacterial organism into those of a pathogenic bacterium was present in the extracted DNA.

32. In the second set of experiments, extracted whole genomic DNA was shown to contain all the genetic information necessary to change a non-cancerous cell into a cancerous cell. One characteristic of cancer cells in culture is that they lose "contact inhibition". Contact inhibition is a phenomenon in which non-cancer cells growing in a petri dish will continue to divide and the new daughter cells will form attachments to the surface of the dish and spread out on the surface, until they touch other cells in the culture. Upon touching other cells, non-cancerous cells stop dividing and become quiescent. Contact inhibition is an important characteristic of non-cancerous cells. Many cancer cells in culture lose their contact inhibition and continue to divide even after touching other cells, lose their firm attachment to the petri dish surface,

and pile up one on top of the other, thereby creating mounds of poorly attached cells.

33. In 1982, three laboratories independently reported that isolated genomic DNA from a cancer cell could convert cultured mouse fibroblast cells that were non-cancerous and showed contact inhibition, into cancerous cells that had lost contact inhibition. (Shih, C. & Weinberg, R. A. Isolation of a transforming sequence from a human bladder sarcoma cell line. Cell 29, 161–169, 1982; Goldfarb, M., Shimizu, K., Perucho, M. & Wigler, M. Isolation and preliminary characterization of a human transforming gene from T24 bladder carcinoma cells. Nature 296, 404–409, 1982); Pulciani, S. et al. Oncogenes in human tumor cell lines: molecular cloning of a transforming gene from human bladder carcinoma cells. Proc. Natl Acad. Sci. USA 79, 2845–2849, 1982). In these three experiments, genomic DNA was extracted away from the rest of the cellular constituents of cells that had been derived from human cancers. The extracted DNA was applied to cultures of non-cancerous mouse fibroblast cells under conditions that encouraged the cells to take up the naked DNA. A small amount of the human DNA made its way into the nucleus of these non-cancerous cells and became incorporated into their chromosomes. The cell cultures were then watched over time. Small areas of heaped-up transformed cells developed on a lawn of otherwise non-transformed contact-inhibited mouse cells. These areas of heaped up cells were isolated, grown up, and DNA was again extracted from these cells. Most of this DNA in fact was made up of mouse cell DNA with a small proportion that was human in origin. The extracted DNA was reapplied to another

lawn of non-transformed mouse cells, which again took up this genomic DNA and once again developed small foci of heaped-up cancerous cells on a lawn of otherwise non-cancerous contact-inhibited mouse cells. These foci could again be isolated, grown, and the DNA extracted and re-applied to a new lawn of untransformed cells. This approach of repeated serial transformation of the mouse cells by total genomic DNA extracted from transformed foci led to the discovery that a particular segment of human DNA was responsible for causing the non-cancerous mouse cells to become cancerous and lose contact inhibition. The serial transformation with extracted total cellular DNA in effect separated the human gene responsible for transformation away from the rest of the human DNA. This DNA was found to contain the human ras (H-Ras) oncogene.

34. These experiments with bacteria and cultured mouse cells clearly demonstrate that the same information in the DNA responsible for the smooth capsule or the cancerous behavior of cultured human bladder cancer cells when inside the organism is present in DNA extracted from that organism.

35. The physical embodiment of a gene is DNA and the information contained within that gene is comprised of the arrangement of the bases in the DNA. That is the same whether the DNA is inside the cell or isolated in a test-tube. To claim otherwise is to confuse a gene with the machinery that regulates how that gene is expressed. Thus, I reject the claim that the genes represented by isolated DNAs that are the focus of this patent are "structurally and functionally distinct" in any

significant way from the genes in DNA found in nature.

THE PRIMARY PURPOSE OF ISOLATING DNA IS TO MAKE AN INFERENCE ABOUT THE DNA IN A PERSON'S BODY

36. In paragraphs 138 and 139 of his Declaration, Dr. Kay argues that isolated DNA:

> "...acquires new properties not shared by its native counterpart...Native DNA does not have the chemical, structural, functional properties that make isolated DNA so useful to the molecular biologist. Native DNA cannot be used as molecular tools, such as probes and primers, and cannot be used to detect mutations. Nor can it be used in sequencing reactions to determine the structure of a DNA molecule."

37. The argument that the isolated DNA can be put to uses that the native DNA cannot forms important underpinning to the arguments the Defendants make in their "Memorandum of law (1) in support of their motion for summary judgment and (2) in opposition to plaintiffs' motion for summary judgment" in which they refer to the case of *Parke -Davis & Co. v. H.K. Mulford Co.* concerning the patentability of a purified natural product, in this case, adrenaline, and quote Judge Hand who stated:

> "even if [the adrenaline] were merely an extracted product without change, th*ere is no rule that such products are not patentable.* [The Patentee] was the first

> to make [adrenaline] available for any use by removing it from the other gland-tissue in which it was found, and, *while it is of course possible logically to call this a purification of the principle, it became for every practical purpose a new thing commercially and therapeutically.* That was a good ground for a patent."

Once again referring to the analogy of gold mining, trace amounts of gold embedded in gangue rock cannot be used for making jewelry or for applications in electronics, the way purified gold can be used. Nonetheless, gold embedded in gangue rock is still gold and is not transmuted into some other novel substance by virtue of its being extracted and used in ways the gold in ore cannot be used.

39. There is also an important distinction between the case of the purification of adrenaline for commercial or therapeutic use and the isolation of DNA containing the *BRCA1/2* genes for sequencing. The isolation of adrenaline provided a substance that was itself useful for injection into any patient. In contrast, being able to sequence isolated DNA in a test tube in order to find mutations in that isolated *BRCA1/2* gene is by itself of no particular value. The true value only comes from inferring that any mutation found in the isolated material is also present in the DNA of the person from whom the DNA was isolated. This observation underscores that the clinical value of obtaining the sequence and finding a mutation in an isolated segment of a *BRCA1* or *BRCA2* gene relies on the fact that the physical embodiment of a gene is DNA and the

information contained within that gene is comprised of the arrangement of the bases in the DNA, whether the DNA is inside the cell of a particular individual or isolated from that individual and placed in a test-tube.

40. Dr. Kay's argument that "isolated" genomic DNA segments can be used as probes and primers is also mistaken. An isolated genomic DNA segment is too large and cannot be used as a "primer" in any practical applications. Primers are short chains of nucleotides, often approximately 20 basepairs in length but may range up to 100 base pairs in length, that are complementary to a region in the DNA. They are ordinarily used as an anchor point on which DNA synthesis can be initiated by extending the primer, such as in PCR reactions to replicate a segment of DNA. Primers are manufactured; they are not extracted from native DNA. Probes are pieces of DNA or RNA corresponding to a gene or sequence of interest. Probes are labeled either radioactively or with some other detectable molecule, are made single-stranded if they were originally double stranded, and then allowed to form stable base pairing (A with T or U, G with C) with a "target", which is commonly a fragment of DNA or RNA that is complementary to the probe and has been fixed to a solid substrate (such as a membrane or plastic). While it is possible that a segment of genomic DNA the size of a gene such as *BRCA1* or *BRCA2* could be used as a probe, it is never used in this way for any clinical applications.

THE EXONIC SEQUENCES IN cDNA ARE THE SAME AS THOSE OF THE EXONS OF NATIVE DNA AND cDNAS OCCURRING NATURALLY IN THE HUMAN BODY

41. With regards to cDNA, Dr. Kay states in paragraph 154 of his Declaration

> "Thus, contrary to Dr. Leonard's statement that the coding effect of a cDNA is the same as that of the original DNA from which it was originally derived despite having a shorter sequence," alternative splicing can give rise to many different mRNAs from the same native DNA molecule (*see* Leonard, ¶ 75). cDNAs can be prepared from mRNAs as discussed below. However, the cDNA captures that one mRNA from which it was synthesized and not all other splice variants that result from that one gene."

Dr. Kay is correct that more than one type of mRNA, and therefore more than one cDNA, can be made from a single genomic copy of a gene due to alternative splicing. However, it remains true that the exonic sequences present in a cDNA, which are a reflection of which exons were retained in the mRNA after splicing of the primary transcript, are present in the same order as are the exons in the genomic copy of the gene. There may be differences between cDNAs due to gaps or insertions representing exons that were spliced out or retained respectively in some mRNAs and not in others, but there are no inversions or swapping of positions of exon sequence between different cDNAs.

42. In paragraph 164 of his Declaration, Dr. Kay states that

> "an isolated cDNA molecule is an artificial construct that does not exist in the body and hence is structurally and functionally different from both native DNA and RNA."

On the contrary, it has been known for decades that cDNAs in the form of "processed pseudogenes" are natural products and exist in the cells of the body. Processed pseudogenes are double-stranded DNA sequences in the human genome that resulted from the same biochemical process, RNA-templated DNA synthesis (reverse transcription) presumably carried out in our evolutionary past by viruses containing a reverse transcriptase enzyme. These naturally occurring cDNAs were inserted randomly into the human genome and passed down through the generations to the present day. Processed pseudogenes contain largely the same bases, in the same order, as the cDNA made from the mRNA derived from transcription of a gene.

Alignments of a cDNA made from the mRNA of a gene and a processed pseudogene of that gene can be identical over 80-90% of the length of the molecule. Like cDNAs made artificially in a test tube, processed pseudogenes can include segments of the polyA tail, but not the 5' cap, that are typically present in mRNA. For example, my coworkers and I reported in 1984 that 14 cDNA copies of the argininosuccinate synthetase gene exist in the human genome, distributed on 12 different human chromosomes (Su TS, Nussbaum RL, Airhart S, Ledbetter DH, Mohandas T, O'Brien WE, Beaudet AL Human chromosomal assignments for 14 argininosuccinate synthetase pseudogenes: cloned DNAs as reagents for cytogenetic analysis. Am J Hum Genet. 1984 Sep;36(5):954-64). Thirteen of these pseudogenes contain >80% of the sequence present in the complete mRNA and, over this shared region, more than 85% of the bases are identical. Attached as an Exhibit is a diagram showing just one of the argininosuccinate synthetase pseudogenes that aligns with 80% of the cDNA of argininosuccinate synthetase mRNA (NM_000050.4 in Genbank at NCBI) with over 90% identity of the nucleotides between the cDNA and the pseudogene.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Robert L. Nussbaum

Robert L. Nussbaum, MD

Executed on January 18, 2010

EXHIBITS 1, 2

[EXHIBITS 1, 2 OMITTED]

[Supplemental Declaration of Christopher Mason, filed January 20, 2010] [Caption Omitted In Printing]

I, Christopher E. Mason, declare under penalty of perjury:

1. I previously submitted a declaration in this case on August 20, 2009. I am currently Assistant Professor of Computational Genomics at Weill Cornell Medical College in New York City. I also hold an appointment at the tri-institutional training program on computational biology and medicine between Rockefeller University, Memorial Sloan-Kettering Cancer Center, and Cornell University. I perform research, publish, and teach courses on whole genome sequencing and methods for cataloguing and characterizing human genetic variants ranging from single cells to whole tissues, in normal development and in cancer.

2. I have read some of the submissions made by Myriad in this case. Specifically, I have read the Myriad brief, the declaration of Dr. Kay, and Myriad's Statement of Material Facts. I am submitting this supplemental declaration in response to those documents.

3. Naturally occurring genetic variants contribute to the phenotypic uniqueness of each individual and also create susceptibility to certain diseases, such as breast or ovarian cancer. These variations may be small, such as a single-nucleotide variant (SNV), such as changing an A to a G at one position. Also, genetic variants may be very large, such as the removal/insertion of hundreds of bases or the complete deletion/duplication of an entire gene.

Consequently, genetic variants that can influence a person's susceptibility to disease may involve an extraordinarily large range of possibilities, and each individual is likely to harbor entirely novel (*de novo*) variants. As a result, a patent on a genetic sequence can include (and if it wishes to preclude sequencing of the gene, must include) *any* possible variants found by the patent applicants as well as claims on any *de novo* variations or fragments of the claimed sequence that might be found in the future. Recent research has shown variants at about one out of every 500 base pairs (bp), meaning that the BRCA1IBRCA2 genes are likely to hold dozens or hundreds of variants.

4. The natural variation inherent to the human genome makes patenting a specific locus of the human genome impossible, since any genomic locus is slightly different in every person, changes during a person's life and in each tissue, and changes within the human species throughout time. The very flexibility the defendants seek in their claims for cataloging all BRCA1/BRCA2 variants undermines their ability to claim a single molecule, since that molecule will vary from one individual to the next.

5. Among defendants' claims is claim 6 from patent '282.

> 1. *An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.*
>
> 2. *The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ 1D NO:1.*

> *6. An isolated DNA having at least 15 nucleotides of the DNA of claim 2.*

6. Claim #6 is so broad that it includes at least 4% and as much as 100% of the genes in the human genome.

7. I used a Perl algorithm[1] to determine if any 15 contiguous nucleotides (15mer) present in the BRCA1 cDNA from claim 2 (SEQ ID NO:1) were also present in other genes' cDNAs. I used the NIH CCDS (National Institute of Health Consensus Coding Sequence) database, which maintains a well-defined set of cDNAs for 18,646 genes. I observed that 4% (716/18,646) of the cDNAs from genes in the human genome contain an exact match to one or more 15mer from SEQ ID NO:1, including, of course, BRCA1 (bold). These genes are the following:

> ABCA10, ABCB4, ABCB7, ABCC1, ABCC5, ACCSL, ACER2, ACER3, ACSL3, ACSM3, ACTL6A, ACVR1B, ADAM22, AGAP2, AGAP3, AGFG1, AGGF1, AHNAK, AIM1L, AKAP9, AKR1B10, AKR1B15, ALPK1, ALS2, AMIGO2, ANKRD11, ANKRD13D, ANKRD31, ANKRD43, AP1S2, AP3M2, APOB, ARAP3, ARHGAP10, ARHGAP24, ARHGEF10L, ARHGEF12, ARHGEF15, ASB11, ASB16, ASPM, ATAD5, ATE1, ATG16L1, ATM, ATP1A1, ATP6V1D, ATR, B3GALTL,

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[1] The algorithm utilized the the 5,914bp BRCA1 cDNA from the '282 patent and the CCDS latest release (January 3, 2010) from the NIH's site: ftp://ftp.ncbi.nih.gov/pub/CCDS/current_human.

BAIAP2, BANK1, BAZ2B, BBS12, BCAT2, BCL9L, BCORL1, BDP1, BEND6, BEND7, BOD1L, BRCA1, BRD9, BRPF1, BRWD1, BTN1A1, BUB1, C10orf79, C10orf96, C14orf183, C14orf45, C16orf54, C16orf88, C17orf65, C17orf70, C18orf19, C18orf55, C1orf101, C1orf112, C1orf114, C1orf187, C1orf26, C1orf59, C1QTNF1, C20orf72, C2orf16, C2orf42, C2orf44, C2orf74, C3orf30, C5orf23, C6orf167, C6orf203, C7orf58, C7orf72, C8orf44, C8orf86, C9orf95, CABIN1, CABYR, CACNA1S, CAMTA2, CARKD, CASD1, CASK, CASP8, CCDC110, CCDC138, CCDC149, CCDC150, CCDC158, CCDC18, CCDC21, CCDC49, CCDC65, CCDC66, CCDC82, CCDC83, CCND3, CCT3, CD2BP2, CD59, CDC123, CDCP1, CDK2, CDR2L, CEACAM19, CECR5, CENPB, CENPE, CEP110, CEP152, CEP78, CHD7, CHIC1, CHRFAM7A, CHRNA7, CIC, CIZ1, CKAP4, CLCNKA, CLCNKB, CLK1, CLTC, CMBL, CMTM4, CNGA1, CNR1, CNTNAP2, COBLL1, COG1, COL15A1, COL4A2, COL4A6, COL7A1, CORO1A, COX7A2L, CPD, CRIM1, CRP, CSNK2A2, CSPP1, CTR9, CUL4B, CUX1, CXCL17, CYC1, CYP3A43, DAZ1, DAZ2, DAZ3, DCHS2, DCP1B, DCTN1, DDB1, DDX20, DDX46, DDX60L, DEK, DGKQ, DHX37, DIP2A, DIRAS3, DMRTC2, DMTF1, DNAH1, DNAH12, DNAH2, DNAH5, DNAH6, DNAJC10, DNAJC13, DNAJC2, DNTTIP2, DOCK11, DOCK4, DOCK6, DOK1, DOPEY2, DPEP1, DPYD, DRG1, DSC3, DST, DYNC2H1, DYTN, E2F1, EFEMP2, EFHA2, EIF2AK3, EIF2S1, EIF2S2, ELF1, ELMO3, ELOVL2, ELOVL3, ELP2, EMILIN2, EMILIN3, ENG, ENOX1, ENPP3, ENPP6, EPHX2, ERLEC1, ESCO2, ETAA1, EXOC3L, EXOG, EXPH5, EYA3, EYS, F13B, FAAH, FAM102B, FAM116A, FAM123B, FAM135B, FAM13A, FAM151B, FAM160B2, FAM161A, FAM179B, FAM185A, FAM186A, FAM193B, FAM22F, FAM22G, FAM57B, FAM5B, FAM82A2, FAM9A, FANCG, FAT2, FBXO21, FBXO38, FBXO42, FBXW5, FCGBP, FCN3, FCRL5, FER1L6, FHOD3, FIS1, FLJ23834, FLJ32810, FNDC7, FOS, FRYL, FSIP1, FUT9, GAL3ST4, GALC, GAPDH, GDF10, GEMIN5, GMIP, GNPAT, GOLGA3, GOLGA4, GOLGA8E, GOLGA8F, GOLGA8G, GOLGB1, GPAM, GPATCH1, GPATCH4, GPR56, GPR98, GRAMD2, GRIA2, GRK4, GSTCD, GTF2A1, GTF3C4, HABP2, HCLS1, HDLBP, HEATR5B, HEPHL1, HERC2, HERC6, HGF, HHAT, HIP1, HIST4H4, HLX, HMCN1, HNRNPA2B1, HNRNPC, HNRNPCL1, HSCB, HSP90AA1, HSPA8, IFI16, IGDCC4, IGF1, IGFBP4, IGSF21, IGSF9, IKZF3, IMMP1L, IMPG2, INTS6, INTS8, IPO8, IQCD, IQCF2, ITGA1, ITGA4, ITIH4, ITSN1, IVNS1ABP, JRKL, KBTBD7, KCND1, KCNJ6, KCNK1, KCNQ1, KCNQ5, KCTD20, KDM4A, KIAA0652, KIAA1009, KIAA1109, KIAA1244, KIAA1267, KIAA1429, KIAA1549, KIAA1683, KIAA1731, KIAA2026, KIDINS220, KIF15, KIF16B, KIF21A, KIF5B, KIR3DL2, KRI1, KRT8, LAMA4, LAMB3, LARP1B, LARP7, LCP1, LDHB, LEO1, LHCGR, LIG1, LPGAT1, LRP1B, LRRC45, LRRC8D, LSG1, LYPD6B, MAGEB10, MAN2A2, MAP1A, MAP3K12, MAP3K2, MAP3K7IP1, MAP7D2, MAP9, MASP1, MAST4, MCCC1, MDN1, MED12L, MED13, MED7, MET, METAP2, MIA2, MICALCL, MICALL2, MIER3, MINK1, MKL2, MLH3, MRPL55, MRPS10, MRPS25, MS4A8B, MTERF, MTIF2, MTUS2, MUC15, MUC6, MYCN, MYH1, MYH15, MYH3, MYLK, MYO15A, MYO1B, MYO3B, MYO5C, N4BP2, NAGPA, NAP1L2, NAT10, NAV1, NBEAL1, NCOR1, NDE1, NDEL1, NEK1, NFATC2IP, NFKBIL2, NFXL1, NGDN, NGFR, NIN, NKAPL, NKTR, NLRP13, NLRP2, NLRP9, NMBR, NOC3L, NPAS4, NR3C2, NT5C1B, NTRK3, NUDT5, NUP153, NUP85, ODZ3, OFD1, OR13F1, OR2A1, OR2A12, OR2A14, OR2A5, OR2M2, OR2M7, OR2T1, OR2T6, OR4C3, OR4F16, OR4F21, OR4F29, OR4F3, OR5B21, OSBPL3, OTOF, PABPC1, PADI1, PAK1, PAN2, PCDHA10, PCDHA11, PCDHA12, PCDHA13, PCDHA6, PCDHAC1, PCDHAC2, PCDHB15, PCLO, PDCD4, PDCD6IP, PDE6C, PDS5A, PDZD2, PDZD4, PGK1, PHEX, PHF20, PHF23, PHKA1, PIGN, PIH1D2, PIK3AP1, PIK3C2A, PIKFYVE, PITPNM3, PKD1L2, PLB1, PLCZ1, PLEKHM1, PNMA5, POLQ, PPP1R10, PPP1R3A, PPP1R3B, PPP2R3C, PRDM5, PRKAG2, PRODH2, PROX1, PRPF40A, PRPS1, PSPH, PTDSS2, PTK7, PTPDC1, PTPRN, PUS3, RAB11FIP5, RANBP2, RASAL1, RAVER1, RBM20, RBM25, REV3L, RGN, RGS3, RIMBP3, RIMBP3B, RIMBP3C, RNF14, RNF20, RNPC3, ROD1, ROR1, RORB, RPGRIP1, RPL13A, RPS6KA1, RRBP1, RSPRY1, RXFP3, SAMD4A, SAPS1, SBNO1, SCAND3, SCG3, SDK1, SEBOX, SECISBP2, SEMA5A, SEMA6C, SENP7, SERPINB5, SERPIND1, SERPINH1, SESN1, SETD5, SF3A1, SFRS18, SFRS4, SGCB, SGCG, SGOL2, SH2D3A, SH3D19, SHPRH, SIGLEC10, SIM2, SIN3B, SIPA1, SKAP1, SLC15A4, SLC1A6, SLC30A2, SLC38A4, SLC39A10, SLC3A1, SLC43A2, SLC5A3, SLC8A3, SLCO2A1, SLIT3, SLU7, SMC4, SMC5, SMYD3, SNAPC4, SNX6, SON, SORBS3, SOX6, SP100, SP140, SPAG16, SPATA16, SPPL2A, SRCAP, SRP54, SRPK2, SRRM2, SRRM4, SSBP2, STAG2, STIM1, STK10, STK35, STOX1, STOX2, STRADA, SUV420H2, SVIL, SYNE2, SYNGAP1, SYNRG, SYT1, SYT13, TAF3, TANC2, TAOK3, TARS, TARS2, TAS1R1, TBC1D8B, TCOF1, TDRD6, TESC, TET3, TEX2, TFAP2B, TFB1M, TFE3, TGS1, THUMPD2, TIGD1, TLR6, TMC4, TMEM161B, TMEM168, TMEM176B, TMEM232, TMEM99, TMF1, TMPRSS11E, TMPRSS7, TNRC6B, TP53TG5, TPST2, TPX2, TRAF6, TREM2, TRIM33, TRIM60, TRIM61, TRNT1, TRPC1, TRPM3, TSPAN12, TSPAN13, TSPAN3, TTC28, TTLL7, TWF1, TWISTNB, UBAP2, UBR3, UEVLD, ULBP1, UROD, USP39, USP42, UTP14A, UTP20, VASN, VCPIP1, VPS8, VSX1, VWF, WDR33, WDR54, WDR75, WDR87, XRN1, ZADH2, ZBTB32, ZBTB34, ZC3H12B, ZC3HAV1, ZCCHC17, ZCCHC6, ZDBF2, ZDHHC12, ZEB1, ZFC3H1, ZFHX4, ZFP1, ZMYM4, ZMYM6, ZNF133, ZNF195, ZNF238, ZNF25, ZNF322B, ZNF34, ZNF407, ZNF438, ZNF469, ZNF521, ZNF530, ZNF546, ZNF655, ZNF709, ZNF732, ZNF772, ZNF804B, ZNF84, ZSWIM4.

8. Since the definition of the BRCA locus from '282 is broad enough to include the entire gene, I then used the same Perl algorithm (see Paragraph 7) to determine if any 15 contiguous nucleotides (l5mer) present in the BRCA1 cDNA from claim 2 (SEQ ID NO:1) were present in any gene in the genome. Using

the '282 definition of a genetic locus and the University of California Santa Cruz Genome Browser

(http://genome.ucsc.edu/) database, I extracted all full-length genetic loci from any known gene (UCSC official genes) in the human genome (build 37), including one kilobase of upstream sequence to represent regulatory regions. I observed that 99.999% (66,794/66,803) of the genes in the human genome contain an exact match to one or more 15mer from SEQ ID NO:1, including BRCA1. On average, each gene contains 595.3 instances of one of the 15mers listed in SEQ ID NO:1. The only nine genes without any of the 15mer sequences were: uc002tlg, uc003arw, uc002ahy, uc003wbc, uc002bsc, uc002btr, uc003vzz, and uc002vvu.

9. Claim #6 does not appear to be limited to 15 *consecutive* nucleotides. Re-running the analysis for any 15 nucleotides from SEQ ID #1 in any order results in every gene in the human genome (100%) being covered by claim #6.

10. Claim #1 and #2 of '282 are so broad that they can include up to 100% of the genes in the human genome. Because fragments of the BRCA1 gene can also be informative about susceptibility to disease, the defendants also sought claims on DNA molecules or fragments of DNA molecules with 'substantial homology.' See patent '282 (19:26-50)(emphasis added):

> "BRCA1 Locus," "BRCA1 Gene," "BRCA1 Nucleic Acids" or "BRCA1 Polynucleotide" each refer to polynucleotides, all of which are in the BRCA1 region, that are likely to be

> expressed in normal tissue, certain alleles of which predispose an individual to develop breast, ovarian, colorectal and prostate cancers. Mutations at the BRCA1 locus may be involved in the initiation and/or progression of other types of tumors. The locus is indicated in part by mutations that predispose individuals to develop cancer. These mutations fall within the BRCA1 region described infra. The BRCA1 locus is intended to include coding sequences, intervening sequences and regulatory elements controlling transcription and/or translation. The BRCA1 locus is intended to include all allelic variations of the DNA sequence.
>
> These terms, when applied to a nucleic acid, refer to a nucleic acid which encodes a BRCA1 polypeptide, fragment, homolog or variant, including, e.g., protein fusions or deletions. The nucleic acids of the present invention will possess a sequence which is either derived from, or substantially similar to a natural BRCA1-encoding gene or one having **substantial homology** with a natural BRCA1-encoding gene **or a portion thereof**. The coding sequence for a BRCA1 polypeptide is shown in SEQ ID NO:1, with the amino acid sequence shown in SEQ ID NO:2.

11. The patent defines the terms bolded in the prior paragraph:

> "Substantial homology or similarity". A nucleic acid or fragment thereof is "substantially homologous" ("or substantially similar") to another if, when optimally aligned (with appropriate nucleotide insertions or deletions) with the other nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 60% of the nucleotide bases, usually at least about 70%, more usually at least about 80%, preferably at least about 90%, and more preferably at least about 95-98% of the nucleotide bases.

Alternatively, substantial homology or (similarity) exists when a nucleic acid or fragment thereof will hybridize to another nucleic acid (or a complementary strand thereof) under selective hybridization conditions, to a strand, or to its complement. Selectivity of hybridization exists when hybridization which is substantially more selective than total lack of specificity occurs. Typically, selective hybridization will occur when there **is at least about 55% homology over a stretch of at least about 14 nucleotides**, preferably at least about 65%, more preferably at least about 75%, and most preferably at least about 90%. See, Kanehisa, 1984. The length of homology comparison, as described, may be over longer stretches, and in certain embodiments will often be over a stretch of at least about nine nucleotides, usually at least about 20 nucleotides, more usually at least about 24 nucleotides, typically at least about 28 nucleotides, more typically at least about 32 nucleotides, and preferably at least about 36 or more nucleotides.

12. Because of this low threshold of homology, any 55% homology of 14 nucleotides is now any 8 nucleotides from BRCA1 cDNA. Also, homology could include any 9-13 nucleotide sequence with insertions and deletions. Utilizing the same algorithm from above, the conclusion is that 100% of the genes in the human genome have at least one 8mer from the BRCA1 cDNA.

13. The patents define "isolated" DNA as something that encodes a BRCA1 protein or a fragment thereof. See patent '282, 19:5. If so defined, very small segments of DNA can encode a fragment of the BRCA1 protein.

14. The contention by the Myriad defendants that "isolated" DNA acquires new properties which are different in kind is erroneous. They claim isolated DNA can be used as a probe. They rely on the Alberts et al. text for several of their definitions. This text defines probe as follows: "a defined fragment of RNA or DNA, radioactively or chemically labeled, used to locate specific nucleic acid sequences by hybridization." (Alberts, Bruce, et al. Molecular biology of the Cell, 3rd ed. New York City: Garland Publishing. 1994. p.G-19). According to this definition, isolated DNA by itself cannot be used as a probe, as it requires subsequent chemical modifications, such as fluorescent or biotinylated tags, to allow the DNA to be visualized and therefore serve as a probe. If what defendants mean by a "probe" is any sequence of DNA or RNA that binds to a complementary sequence, then this would include

every segment of the human genome in the cellular milieu or in an isolated state.

15. Also, for a DNA probe to actually "probe" another region of the genome, it utilizes the same functional and chemical properties as the native DNA, which is hybridization of the complementary base pairs through hydrogen bonds. For the probe to actually work, it is **necessary** that the isolated DNA still functions in the **exact** same capacity as the native DNA, wherein complementary bases can anneal, or hybridize, to each other.

16. Myriad claims isolated DNA can be used as a primer. This claim is incorrect. A portion of the isolated DNA may be used as a primer. I know of no instance in the scientific literature of a full length cDNA having been used as a primer. cDNA of the length specified in SEQ ID NO:1 would very likely fold into secondary structures and inhibit any reaction. Indeed, the patent itself recognizes the need to design a pair of short primers from the sequence itself. Patent '282, claim 16.

17. A primer is simply a short, single-stranded segment of DNA or RNA (usually 15-30 nucleotides) that is complementary to a given DNA sequence and that can be used to initiate a sequencing reaction or replication. A segment of native DNA can also be used as a primer for DNA replication to occur. In both the native and isolated state, the same functional and chemical properties of the DNA allow for these reactions to occur namely, the binding of complementary sequences to initiate a reaction. This also occurs in the body (Figure 1).

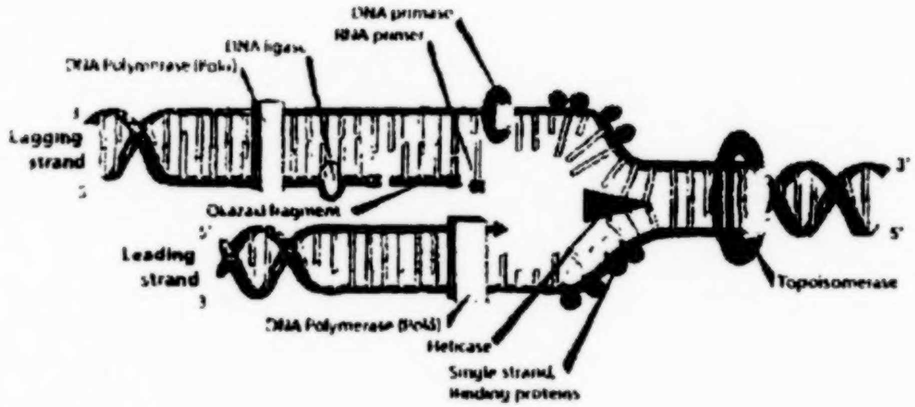
DNA primase
RNA primer
DNA ligase
DNA Polymerase (Polα)
3'
Lagging strand
5'
Okazaki fragment
5'
Leading strand
3'
DNA Polymerase (Polδ)
Helicase
Single strand binding proteins
3'
5'
Topoisomerase

Figure 1 – DNA replication The new DNA strand and Okazaki fragments serve as a primer for DNA replication. From Mariana Ruiz.

18. My prior declaration (paragraphs 27-29) discussed the process of making cDNA in a laboratory. cDNA can be generated in the laboratory using routine, standard techniques. Defendants assert that cDNA is different in kind from what exists in the body. This is incorrect. Both DNA and cDNA are described by the same series of nucleotide bases these bases are the same chemical structure in both DNA and cDNA and in the same sequential order in both, much like the pages in a book are still in the same order even when one page is removed. Moreover, the same process for making cDNA in the laboratory, using the same enzyme, occurs naturally in the body. In the scientific literature, these naturally occurring cDNAs are created through a process called retrotransposition. In this process, a portion of a normal mRNA transcript from a gene is reverse transcribed back into DNA (naturally creating a cDNA) and is often re-inserted back into the genome. These converted, or retrotransposed,

genes often create a cDNA copy of the mRNA, and as such, they are usually inserted back into the genome with a poly-A tail, no introns and no regulatory elements. These naturally occurring cDNAs are structurally, functionally, and chemically identical to cDNAs made in the laboratory. These cDNAs, if then inserted back into the genome, are called pseudogenes. Most importantly, a segment of the claimed cDNA already exists in the human genome, known as BRCA1 Psuedogene1 (also called BRCA1P1). These processes that generate pseudogenes are not done by scientists, but naturally occur inside the cells of living beings.

19. Defendants are correct that cDNA can be made in a laboratory. The methods for doing so are routine, standard methods. Those methods are utilized every day by scientists all over the world to make cDNA from other genes and other segments of DNA. There is also nothing unique in making BRCA1 or BRCA2 cDNA; the same standard methods are merely applied to that pa1licular region of the DNA. When cDNA is made in a laboratory, the result is usually fragments of cDNA that are not as long as a full gene. (Note, the same is true for naturally occurring cDNA - these often occur as fragments of the full length gene). But, contrary to defendants' implications, scientists sequencing the cDNA do not stick the fragments together. A simple computer program, used every day by scientists all over the world, can determine the sequence even though the cDNA is fragmented. Thus, the full cDNA sequence described in the patents would rarely exist as one intact chain in the laboratory. The same is true of isolated DNA.

20. Defendants argue that cDNA is different from "native DNA" because it does not contain regulatory regions. However, cDNAs may contain untranslated regions (UTRs) which contain regulatory structures that are targeted by cellular machinery to regulate the translation of the mRNA. As such, while cDNA generally does not contain all regulatory sequences or structures needed for transcription, it can contain some regulator elements.

21. DNA is not generally described according to the sugars and phosphates that make up its backbone. As the patents in this case make clear, DNA is described according to the sequence of nucleic acids, which contain all of the relevant information about the product that the gene creates. In this respect, its description is entirely different from H_20 as a description of water. For example, H_20, HOH and OH_2 all describe and represent the exact same molecule; conversely TAA, ATA and AAT encode entirely different amino acids. TAA instructs the body to stop translation. ATA codes for isoleucine. AAT codes for asparagine.

22. The chemical structure of nucleotides outside the body is the same as the chemical structure of nucleotides inside the body. Defendants argue that DNA in the body can be methylated, i.e. that it can have additional chemical groups attached to it. That statement is true. However, DNA also appears in the body in a non-methylated state. Also, many isolation techniques maintain the methylated state of the nucleotides after they have been removed from the body. Thus, both native DNA and isolated DNA can me methylated or un-methylated.

23. Defendants argue that DNA in the body is never "free floating." That argument is incorrect. During replication inside the body, a fragment of the DNA is free floating, with no proteins or other molecules attached to it. The body unwinds DNA and separates the strands when it duplicates the genes during mitosis and meiosis (Figure 1) and when it transcribes the genes during protein synthesis. At that time, segments of the DNA strands are free floating.

I declare pursuant to 42 U.S.C. §1746, under penalty of perjury under the laws of the United States that the foregoing is true and connect to the best of my knowledge and belief.

/s/ Christopher E. Mason

Christopher E. Mason

January 19, 2010

[Declaration of Roger D. Klein, filed January 20, 2010] [Caption Omitted In Printing] [Exhibit 1 Omitted]

I, ROGER D. KLEIN, MD, JD, certify under penalty of perjury that the following is true and correct:

1. I am currently Medical Director of Molecular Oncology at BloodCenter of Wisconsin, and Clinical Assistant Professor in the Department of Pathology at Medical College of Wisconsin. I previously served as Medical Director of Molecular Diagnostics at H. Lee Moffitt Cancer Center, and Assistant Professor in the Department of Oncologic Sciences at University of South Florida Medical School. The statements herein represent my views as an individual and not those of BloodCenter of Wisconsin or Medical College of Wisconsin.

2. I earned my undergraduate and medical degrees at Case Western Reserve University (OH, USA), and completed an internship in internal medicine at a Case Western Reserve University School of Medicine affiliated hospital. I completed residency training in Laboratory Medicine (Clinical Pathology) and fellowships in Medical Microbiology and Molecular Genetics at Yale University School of Medicine (CT, USA). I then completed a fellowship in Molecular Genetic Pathology at Mayo Clinic (MN, USA). In addition, I earned a law degree (J.D.) from Yale Law School, and am licensed to practice law in the District of Columbia and Ohio.

3. I am board-certified in Clinical Pathology and Molecular Genetic Pathology. I am a member of the Centers for Disease Control (CDC) sponsored

Evaluation of Genomic Applications in Practice and Prevention Working Group (EGAPP), and am a consultant to the U.S. Food and Drug Administration's (FDA) Clinical and Molecular Genetics Advisory Panel. I have served on the College of American Pathologists' Biochemical and Molecular Genetics' and 'Point-of-Care Testing' Resource Committees, and am currently a member of the College of American Pathologists' Molecular Oncology Resource Committee. I also serve on the Association for Molecular Pathology's Professional Relations and Economic Affairs and Committees, and am a member of the Clinical Laboratory Standards Institute's (CLSI) Subcommittee on Establishing Molecular Testing in Clinical Laboratory Environments. In addition, I am a member of the Editorial Advisory Board of the Journal Pharmacogenomics (Future Science).

4. My academic and clinical efforts focus on the translation of genetic knowledge into clinical diagnostic tests for the evaluation and management of hematopoietic and solid tumor malignancies and hereditary cancer syndromes. This work includes the assessment of the clinical validity, clinical utility and the optimal and appropriate use of molecular genetic tests. In addition, I have an active research program involving the ethical, legal and social implications of the Human Genome Project, with particular emphases on the areas of intellectual property and the regulation of *in vitro* diagnostics and clinical laboratories. I have multiple publications in these areas.

5. In my medical practice I oversee the design, validation, and performance of genetic tests for

inherited disorders and cancer on patients' blood cells and tissue. I analyze the genetic data that arises from such tests and provide patient-specific reports that interpret this information and place it into clinical context. In addition, I advise ordering physicians on the appropriate use of genetic tests generally and for individual patients, and provide patient-specific consultation about the meaning of the genetic information we provide.

6. Attached as an exhibit is my curriculum vitae.

7. The statements herein describe the molecular structure and biological role of DNA and messenger RNA (mRNA), and specifically address the role and function of DNA and mRNA in genetic testing. These statements also address the mental acts of associating or correlating genetic variation with clinical phenotypes such as the presence of, predisposition to, and prognosis of human disease. For the purposes of this declaration, I define genetic testing as the interrogation of a patient's cellular DNA to determine its nucleotide sequence followed by comparison of the patient's DNA sequence to that of a reference or "normal" sequence, wherein the presence of a deviation from the reference or normal sequence is associated or correlated with a clinical phenotype as set forth in the preceding sentence.

DNA IS AN INFORMATIONAL MOLECULE

8. DNA contains within its molecular structure the genetic information necessary to specify most if not all aspects of embryogenesis, development, growth, metabolism, and reproduction. DNA provides the blueprint for our highly organized, intricate, complex internal structures, and the template for the

complex molecules that allow us to extract, transform, and utilize the energy that is present in our environment. Thus, first and foremost DNA is an informational molecule. DNA has the ability to store and transmit enormous quantities of information. This information is stored in the sequence of adjacent bases within the DNA strand through what is termed the "genetic code." For a DNA molecule that is "N" bases long, there are 4^n possible DNA sequences.

9. DNA is a chemical compound. However, its chief biological role is as an informational molecule. DNA is unique among biological molecules in its ability to store vast quantities of information and to transmit that information to daughter cells through self-replication. The information contained within the DNA sequence is used generate proteins that are assembled from amino acids. The sequence of amino acids in proteins is integral to their physical structure and biological functions. The genetic code specifies a protein's amino acid sequence. DNA is "transcribed" into mRNA. Messenger RNA carries the information stored in DNA to sites in the cell where the information can be "translated" into proteins on "organelles" called "ribosomes."

10. By comparison, the molecule adrenaline is a signaling chemical that acts on target cells distant from its site of manufacture in the adrenal gland. Whether internally produced or exogenously administered as a drug, adrenaline is carried by the blood to a and P-adrenergic receptors on the surface of its cellular targets, where it non-selectively stimulates these receptors. The stimulated a and 3-adrenergic receptors in turn activate "second messengers," leading to a cascade of enzymatic

reactions that mediate adrenaline's effects. The adrenal glands release adrenalin in response to danger or stress. Adrenaline provides a *non-specific* fight or flight signal that leads to increases in the rate and strength of heart contractions and the constriction of blood vessels, thereby raising blood pressure. Adrenaline also causes expansion of the diameter of airways within the lungs. Adrenaline causes the mobilization of glucose and free fatty acids. Through these and other effects, adrenaline increases the supply of oxygen and glucose to the brain and muscles, while diverting blood away from less urgent processes like digestion. If DNA is likened to a building's blueprint, adrenaline is analogous to the electric signal that turns on the building's furnace in response to a drop in temperature.

11. Unlike DNA, adrenaline is continually produced and degraded. Adrenaline does not encode for the design of human organs like the brain, heart, lungs, or kidneys. Adrenalin does not specify the amino acid sequences of the proteins from which the human body is constructed. Adrenaline does not even store information that tells heart cells how to beat faster or blood vessels to narrow. In contrast to individuals' nucleotide sequences, adrenaline's protein sequence does not vary from person-to-person in its essential chemical features. Naturally occurring adrenaline is a general signaling molecule that exerts its effects through chemical action in a manner analogous to that of exogenously administered drugs.

12. A nucleotide sequence is the linear order of the base pairs of the DNA molecule and its embedded

genes. Genes are regions of the DNA that encode for a functional product. The nucleotide sequences in the coding regions of genes specify the amino acid sequences of the proteins they generate through the genetic code. The order of the nucleotides is of prime importance, because within this order is contained the genetic code, the information that directs human cells to grow, to differentiate into specialized structures, to divide, and to respond to environmental changes. Nucleotide sequences cannot be equated to chemical formulas that represent chemical compounds (e.g. H_2O, NH_3) because such chemical formulas are merely a shorthand way of listing a molecule's constituent atoms and their respective numbers. All substances, both animate and inanimate, are composed of molecules. Atoms are fundamental units of matter that are the building blocks of molecules. All molecules can theoretically be represented by their chemical symbols. For example, the nucleotide adenylate mono phosphate (AMP) which contains adenine as its base is composed of 10 carbon atoms, 12 hydrogen atoms, 5 nitrogen atoms, 6 oxygen atoms, and 1 phosphorous atom and can be written as $C_{10}H_{12}N_5O_6P$. Similarly, this shorthand could be used to describe the atomic (elemental) structure of DNA. However, the complexity of the DNA molecule and its constituent bases renders such depictions impractical, particularly in light of the limited utility this information would provide. By contrast, DNA sequences store and convey specific information that serves as the blueprints for all of the proteins, cells, and organs that make up the human body. Molecules represent a higher and a much more complex level of organization than atoms. Moreover, DNA is unique among molecules because the linear arrangement of its component nucleotides stores and transmits the genetic code.

13. Most DNA in non-dividing human cells is packaged within the nucleus in structures called chromosomes. However, during cell division and during the generation of gametes (eggs and sperm), DNA unwinds and is separated into individual strands. The individual DNA strands serve as templates for the synthesis of new complementary strands, resulting in duplication of the DNA content (genetic material) of the nucleus. The duplicated genetic material is passed along to the newly formed daughter cells that arise from the process of cell division. The DNA also unwinds during transcription, the process by which the information contained within the DNA is transferred to mRNA. During transcription, one of the DNA strands serves as a template for the generation of mRNA. Messenger RNA carries this information to structures called ribosomes on which proteins are synthesized.

14. A gene is a hereditary unit. The term gene is commonly used to refer to a segment of DNA that encodes for a functional product, usually a protein. Therefore, genes contain discrete units of genetic information.

15. Each DNA strand contains the full informational content of the DNA molecule and serves as the template for the synthesis of a new complementary strand. One of the 2 complementary DNA strands normally serves as a template for mRNA synthesis. Messenger RNA is translated into proteins. The protein amino acid sequence is directly

dependent on the sequences of nucleotide bases in the DNA strand. A protein's amino acid sequence is a key determinant of its structure and function. Thus, mRNA is the essential connecting link between the information contained in the gene, and the specific amino acid sequence of the protein.

16. The language used in the process of translating the information in DNA into protein amino acid sequences is known as the genetic code.

17. Three base pair words (codons) specify the particular amino acid at its specific position in the protein. Because proteins are comprised of 20 amino acids, the codon had to include at least 3 bases (base pairs) to unambiguously specify an amino acid. (There are 4 possible bases at each position in the DNA molecule. if the codon included only 2 base pairs, there would be just 4 x 4, or 16 possible combinations, which would leave too few codons to encode for all 20 amino acids. By contrast, 3 base pair codons have 4 x 4 x 4 = 64 possible combinations, yielding substantially more codons than are necessary to encode for all 20 amino acids.)

18. The excess of codons over the number of amino acids allows for redundancy in the genetic code, which is referred to as degeneracy. This means that some amino acids are encoded for by more than 1 codon (several different codons result in incorporation of the same amino acid in the extending protein chain). Degeneracy may have a biologically protective effect because some of the inevitable mistakes that occur during DNA replication do not alter the amino acid that is incorporated into the protein, and therefore lack functional consequences. The proteins associated

with DNA form a type of scaffolding on and around which the DNA is coiled, but do not encode genetic information. A coiling and uncoiling mechanism allows the body to both store and access the vast amount of information contained in DNA within the extremely small physical space of the cell's nucleus. Thus, many of the proteins to which the defendants refer *can* be viewed as part of DNA's "packaging."

19. DNA provides the blueprint for the cell, the organization of cells, and one could say for human life itself. The information in DNA contains the instructions for the generation of virtually all proteins in the cell. Other protein and nucleic acid elements can influence the expression of the underlying genetic information. For example, epigenetic modification determines whether or to what extent a gene is expressed as protein, and this in turn is governed by the state of the cell and its environment. But the fundamental information needed to produce the protein is contained within the DNA.

20. DNA and its genes are passed from parent to offspring in gamete cells known as eggs and sperm. Essentially one-half of the genes in each individual come from the mother (the egg) and the other half from the father (the sperm).

21. Growth and development of the embryo is produced by cell division. Individual cells copy their essential content and divide into 2 cells, which in turn divide. During embryogenesis, this process of cell replication continues for many cycles. During embryogenesis various genes are turned on and off, causing groups of cells to differentiate into the organs of the body. In many tissues some cells

continue to replicate and divide throughout a person's life.

MUTATIONS ARE ERRORS IN THE GENETIC CODE

22. Rarely, cells make copying errors during replication of the DNA molecule, causing permanent heritable changes in the DNA. Such changes are often referred to as mutations. Errors that occur within the coding sequence of a gene change the information it contains, and may change the amino acid sequence of the protein for which the gene encodes, potentially altering its functional properties.

23. Mutations that are present in egg or sperm cells are passed on to offspring. Many such errors will be harmless to the individual and his or her descendants. Others may be lethal to the growing embryo.

24. Some mutations can be responsible for diseases. Diseases that can be passed on to offspring through the germline are known as genetic or heritable (inherited) diseases. Examples of heritable diseases include Huntington disease and Duchenne muscular dystrophy. For these diseases, virtually everybody who has the associated genetic mutations and has a normal lifespan will eventually suffer from the disorder. People typically have 2 copies of each gene, receiving one copy (termed an allele) from each parent. For some conditions, for example cystic fibrosis, mutations in both alleles are usually necessary to cause the disease. These are termed "recessive" diseases. Other disorders can be caused by only one mutated gene, received from either the

mother or the father. These diseases are termed "dominant."

25. Some mutations greatly increase the likelihood that individuals who carry the mutation will eventually get a particular disease. Thus, they confer a heritable predisposition to the disorder. For some of these diseases, many or most individuals who have the disease gene or genes will get the disease. These diseases are said to have high "penetrance." Such is the case with many disease-causing mutations in the BRCA1 and BRCA2 genes. Mutations in these genes greatly increase the probability that individuals unfortunate enough to have them will develop breast and other cancers.

ISOLATION DOES NOT ALTER THE FUNDAMENTAL DNA BLUEPRINT

26. An isolated DNA molecule is not made by the hand of a scientist; it is separated from its natural environment. Moreover, the genes within isolated, purified DNA often retain their arrangement and physical orientation relative to the original surrounding DNA on the chromosome. Most important, the process of isolating DNA does not alter the informational content of DNA or its embedded genes.

27. Individual genes can be isolated and purified through excision from the chromosome. During genetic testing, genes are not typically "excised" from the chromosome or surrounding DNA. Instead, the gene is left in its native configuration relative to surrounding DNA. However, even a gene that has been isolated through excision is not fundamentally altered because the relevant parts of its sequence,

and therefore its informational content, remain unchanged. Isolation does not in any way alter the fundamental DNA blueprint. The informational content of isolated DNA is not different from that of DNA in the body.

28. For the purpose of genetic testing, DNA isolation is a routine preparatory step that removes the DNA from its environment so as to allow us to read gene sequences using current diagnostic methods. Specifically, DNA isolation allows us to make the millions of copies of the coding regions of individual genes that are required by contemporary sequence reading instrumentation. DNA isolation is a routine procedure that is commonly performed using automated instruments or off-the-shelf kits. DNA isolation does not necessarily change the configuration, position, or arrangement of genes relative to surrounding segments of DNA within the native chromosome. Although chromosomal DNA strands may break as a byproduct of the extraction process, less rather than more breakage is generally favored for testing purposes. Most important, DNA isolation does not alter the nucleotide sequence and therefore the informational content of the genes that are embedded within the DNA strands. If DNA isolation changed these fundamental properties, isolated DNA would be of no practical use in genetic testing.

29. Although "isolation" per se does not normally occur in the body, the body unwinds DNA and separates its strands when it replicates the DNA during cell division and when it transfers the genetic information to mRNA during transcription for use in protein synthesis.

GENETIC TESTING

30. When we perform genetic testing, we extract the DNA and amplify the coding regions and parts of the noncoding regions of particular genes using synthesized primers that hybridize (bind) to the non-coding regions of the genes. When we isolate DNA for genetic testing, we do not "excise" the gene.

31. DNA isolation ("extraction") is a routine procedure that is now performed using kits or automated DNA extraction instruments. In a step termed amplification, we generate large numbers of identical copies of the coding regions and intron-exon boundaries of individual genes contained within the genomic DNA, most often utilizing a process referred to as the polymerase chain reaction ("PCR"). We generate these additional gene copies because current technologies do not allow us to read the DNA at the single molecule level. PCR generates enough copies of the original DNA molecule so that it can be read by contemporary automated sequencers or other gene reading instruments. The patent on PCR, U.S. patent number 4,683,202, is entitled "Process for amplifying nucleic acid sequences," and was issued to Dr. Kary B. Mullis with Cetus Corporation as assignee on July 28, 1987. In 1993, Dr. Mullis was awarded the Nobel Prize in Chemistry for his invention.

32. The claims at issue in this case do not cover diagnostic tools or actual methods used in genetic testing. Nor are they analogous to patents on medical instruments. Rather they claim DNA sequences which are themselves the subject of medical inquiry. Further, they incorporate generic steps in an effort to describe the biological relationships between

mutations in BRCA1 and BRCA2 and the predisposition to cancer in the abstract patent language of a 'process.' However, the key steps in genetic testing, DNA extraction, amplification, and sequencing can now be performed using routine, automated methods. Nevertheless, the defendants claim the exclusive right to read and compare BRCA1 and BRCA2 sequences irrespective of the method used, whether that method is in existence now or will be invented in the future. Correlating a patient's gene sequence with the predisposition to disease is simply another form of medical diagnosis, similar to correlating elevations in blood glucose with diabetes, a heart murmur with mitral stenosis, or the patterns on a pathology slide with a particular type of tumor and its optimal therapy.

33. Automated sequencers reveal the sequence of the nucleotides visually in what is called a chromatogram. That chromatogram is then "read" (by software and visual inspection) to determine a patient's gene sequence.

34. DNA extraction and sequencing are not transformative activities. R-ther extraction is a routine, non-substantial preparatory step that allows for PCR amplification and sequencing. Sequencing is an automated procedure. DNA extraction, PCR, and sequencing do not involve transformations that are central to the purpose of the process of reading a patient's gene sequence. Unlike "tanning, dyeing, making waterproof cloth, vulcanizing India rubber, or smelting ores," which are performed for the purpose of physically transforming substances so as to create what are essentially new materials for their own sake, the purpose of genetic testing is solely to

read the sequence of the DNA, not to transform it into something else. Only in this way can the patient and her physician learn whether a medically relevant mutation is present in her body.

35. In genetic testing, we do not ordinarily generate cDNA. We simply amplify and interrogate a gene contained within extracted DNA for medically important mutations. cDNA is not generally used as a probe or primer in genetic testing because it is too big. Moreover, cDNA typically cannot be used as a primer because primers are generally designed to hybridize to noncoding regions of the gene and cDNA does not contain the noncoding gene regions called introns (primers are placed in noncoding regions of the gene to ensure amplification of both the coding regions and the junctions between the coding and noncoding regions).

36. Knowledge of the medical information contained in the BRCA1 and BRCA2 genes can be extremely important for the management of some breast cancer patients and their relatives who carry the same genetic errors.

37. The information contained within the BRCA1 and BRCA2 genes could be routinely accessed by many pathologists and others skilled in the art using routine automated and semi-automated methods, but for the existence of the BRCA1 and BRCA2 patents. An individual patient's gene sequence can be compared in a straightforward manner to reference sequences that are easily accessible through publicly available databases. This mental act of comparing sequences establishes whether or not the patient's gene sequence varies from normal, and whether or not he or she has a medically relevant mutation.

38. Genetic testing can utilize primers and probes. Using probes and primers in genetic testing, including BRCA testing, does not fundamentally change the DNA. Primers and probes do not alter the underlying DNA sequence that is being read. Therefore, they do not alter its functional properties for the purposes of genetic testing. DNA isolated from the body is not typically used as primers or probes. Primers and probes are most often constructed as synthetic DNA. Primers are typically 18-25 nucleotide bases long. For mutation testing "isolated DNA" itself cannot be used as a probe in most circumstances, because the component DNA molecules are too large. Much smaller sequence fragments are ordinarily used as probes.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Roger D. Klein

Roger D. Klein

Executed on January 19, 2010

EXHIBIT 1

[EXHIBIT 1 OMITTED]

[Declaration of Joseph E. Stiglitz, Ph.D., filed January 20, 2010] [Caption Omitted In Printing] [Exhibit 1 Omitted]

1. My name is Joseph E. Stiglitz. I am University Professor at Columbia University and Chair of Columbia University's Committee on Global Thought. I am also founder and co-president of the Initiative for Policy Dialogue at Columbia.

2. In 2001, I was awarded the Nobel Prize in economics for my analysis of markets with asymmetric information. I was also a lead author of the 1995 Report of the Intergovernmental Panel on Climate Change, which shared the 2007 Nobel Peace Prize.

3. I have been retained by the plaintiffs and their counsel as an expert for this case. I have received no compensation for my services.

4. I received a B.A. from Amherst College and a Ph.D. from the Massachusetts Institute of Technology (MIT) in 1967. I became a full professor at Yale University in 1970, and in 1979 was awarded the John Bates Clark Award, given biennially by the American Economic Association to the economist under 40 who has made the most significant contribution to the field. Prior to coining to Columbia University, I taught at Princeton, Stanford, MIT, and was the Drummond Professor and a fellow of All Souls College, Oxford.

5. From 1993-95, I served on President Clinton's Council of Economic Advisers, and from 1995-97 I served as chairman of the Council. From 1997-2000 I served as Chief Economist and Senior Vice-President of the World Bank. In 2008, I was appointed by

French President Nicolas Sarkozy to chair a Commission on the Measurement of Economic Performance and Economic Progress. I was also chair of the Commission of Experts of the President of the UN General Assembly on Reforms of the International Monetary and Financial System.

6. I founded one of the leading economics journals, *The Journal of Economic Perspectives*, and have authored several books, including *Globalization and Its Discontents* (W.W. Norton June 2001), *The Roaring Nineties* (W.W. Norton), *Towards a New Paradigm in Monetary Economics* Cambridge University Press) with Bruce Greenwald, and *Making Globalization Work* (W.W. Norton and Penguin/Allen Lane, September 2006).

7. I helped create a new branch of economics, "The Economics of Information," which explores the consequences of information asymmetries. I have made major contributions to macroeconomics and monetary theory, to development economics and trade theory, to public and corporate finance, to the theories of industrial organization and rural organization, and to the theories of welfare economics and of income and wealth distribution. In the 1980s, I helped revive interest in the economics of R&D. My work has helped explain the circumstances in which markets do not work well, and how selective government intervention can improve their performance.

8. I have written and spoken extensively on the strengths and limits of intellectual property and its role in stimulating innovation. As member and then chairman of the Council of Economic Advisers, and a member of the Cabinet, one of my responsibilities

was to provide advice on the impact of alternative intellectual property regimes on growth and innovation in the United States. As Chief Economist of the World Bank, one of my responsibilities was to advise countries around the world about the desirability and impacts of alternative intellectual property regimes. This took on increasing significance as the importance of knowledge for development came to be recognized. I have been a keynote speaker at an international meeting of the World Intellectual Property Organization and have been widely engaged in discussions in the United States and abroad. In these various roles, I have had extensive discussions on intellectual property with relevant American, foreign, and international agencies and organizations responsible for the formation of policies concerned with promoting innovation.

INTELLECTUAL PROPERTY: ITS STRENGTHS AND LIMITS

9. Innovation is important; it has transformed the lives of everyone in the world. Intellectual property laws can and should play a role in stimulating innovation. However, the contention that stronger IP rights always boost economic performance is not correct. Poorly designed intellectual property regimes can reduce access to technology and medicine, lead to a less efficient economy, and may even slow the pace of innovation.

10. Intellectual property protection is designed to ensure that inventors, writers, and others who invest their money and time in creative activity receive a return on their investment. Patents give an inventor

the exclusive right to market or use his innovation for a limited period of time, currently 20 years.

11. There are two fundamental problems with the IP system. First, it is based on *restricting the use of knowledge.* Knowledge is what economists call a "public good": everybody potentially can benefit from it, and there is no extra cost associated with an additional person gaining those benefits. Restricting knowledge is thus inefficient. Second, the patent system also grants (temporary) *monopoly power.* Monopoly leads not just to inequities but also to major distortions of resource allocations. The monopoly power generates monopoly rents (excess profits).

12. As a society, we tolerate some monopoly power and some restrictions on the use of knowledge in the belief that they might spur innovation. But the social costs of these distortions and inefficiencies can outweigh the benefits. Patents that impede the dissemination and use of knowledge slow follow-on research, innovations based on other innovations, and can slow overall technological progress.

13. Another fundamental problem is that under the patent system the rewards do not correspond to the marginal social returns. The "marginal social return" is having innovation available earlier than it otherwise would have been. In other words, if the invention was to have occurred anyway, then the contribution of the "inventor" is that it occurred earlier than it would have without the incentives offered by the patent system. The patent system does not reward people on the basis of the marginal social return of their contribution. Instead, it gives the individual or corporation that is first the entire value

of the innovation, which obviously can well exceed the marginal social contribution. As a result, it introduces a distortion.

14. The inefficiencies of the patent system are especially serious in cases where patents are overly broad or improperly awarded on basic knowledge or ideas or natural laws or phenomena. Patents in these categories privatize what is — and should remain — in the public commons.

15. A well-balanced patent system is one that balances the costs of monopolization and the benefits of innovation, by determining what should not be patentable subject matter, limiting the period of patents, requiring disclosure of the details so that others can build on them, and limiting the ability to use patents for "abusive" monopoly power. When patent systems answer, for instance, the questions in the wrong way of what can be patented and how broad patents should be, competition is reduced and innovation is inhibited.

16. Different intellectual property regimes (patent systems) answer these questions differently. The intellectual property regime which is optimal at one time for one country may not be optimal, or even desirable, for another country at another time. Intellectual property is a social construct, not a matter of natural law. As such, the provisions of an intellectual property regime have to be examined, and re-examined, in light of changes in the economy and the evolution of society's innovation system. Such an examination requires a balancing out of the benefits, in terms *of possible* impacts in incentivizing innovation, with the costs, including possible adverse effects on innovation (e.g. resulting from reduced

access to knowledge, impediments posed by "patent thickets," and the adverse effects on innovation association with reduced competition) and the reduced access to the benefits of innovation. There have been many instances where the intellectual property regime has impeded innovation, or would have done so had the government not intervened (as it did in the case of airplanes) or the Courts had ruled differently (as in the case of the development of the automobile).

17. The balancing is reflected, for instance, in the length of life of the patent—a longer patent life might provide increased incentives but would also increase the adverse effects. There is no reason to believe that 20 years represents the "optimal" life of a patent, and in some cases, e.g. orphan drugs, the lifetime has been extended, because of the belief that there is a need for greater incentives.

18. Similarly, one of the reasons for high standards of "obviousness" and "novelty" is that when the standards are low, the induced innovation is limited, while the costs of reduced access to knowledge are significant.

19. There is a broad understanding that in innovative processes, each innovation builds on prior innovation, and that is why there is such concern that the patent system should not reduce follow-on innovations. One of the reasons for strong disclosure requirements is that at least the knowledge that underpins an innovation should be freely available; the hope is that in doing so, advances in knowledge will be promoted, as inventors trade off the costs of the "loss" of secrecy with the benefits conferred by the patent system. Many scholars have concluded

that a system of compulsory licensing (where users of knowledge would pay an appropriately set licensing fee) would be less likely to inhibit follow-on innovations than the current system and at the same time would provide strong incentives for innovation. The U.S. has, so far, not chosen to go that route. This implies that there is a need for even greater care in the determination of what is patentable.

20. The boundaries between what is and is not patentable are, like the other features of the intellectual property regime, an area where judgments have to be made about costs and benefits, and where the boundaries may change with time. The Supreme Court is, for instance, presently reconsidering business process patents — I believe rightly so.

21. In assessing the costs and benefits of issuing patents, it is important to consider broader social costs—access, for instance, to life saving medicines. All governments have recognized this; the US issued a compulsory license for Cipro when confronted with the threat of Anthrax.

22. What is at issue in this case is not a judgment about the patent system as a whole. It is not a judgment about whether the benefits of the patent system exceed the costs. It is not about whether patents can increase incentives, or even, through disclosure, enhance innovation. It is about the desirability of a particular category of patents, those concerning genes. Some countries, including Brazil,[1]

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[1] Lei No. 9.279, de 14 de Maio de 1996, Regula direitos e obrigações relativos à Propiedade Industrial

committed to a strong intellectual property regime, have decided not to allow such patents. Others that allow such patents accompany them with a strong "compulsory license" provision. For example, compulsory licensing is available for researchers in Germany in cases where such licensing is deemed to be in the public interest.[2] In assessing the desirability of this particular category from an economic and social perspective, the issue is not so much whether there are *some* benefits from the issuance of the patent, but whether the benefits exceed the costs.

PATENTS ON HUMAN GENES

23. Genes are the instructions inside each living being that tell it what proteins to produce. Those proteins, in turn, determine growth and affect susceptibility to disease. Knowledge of the genetic code can be of enormous benefit in finding cures and

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(Brazil), *available at* http://www.wipo.int/clea/en/details.jsp?id=515 (Article X (IX) states that "all or part of natural living beings and biological materials found in nature, even if isolated therefrom, including the genome or germoplasm of any natural living being, and the natural biological processes" are not considered to be inventions).

[2] Patentgesetz [Patent Act], Dec. 16, 1980, last amended by Law of October 25, 1994, § 24 ("(1) If the applicant or patentee refuses to permit the exploitation of the invention by another person offering to pay reasonable compensation and to furnish security therefore, such person shall be given authority to exploit the invention (compulsory license) where permission is in the public interest.") Available at: http://www.wipo.int/clea/en/details.jsp?id=984.

developing vaccines. This was one of the reasons that such importance was placed on decoding the entire genetic structure, which was eventually completed in 2003 by the publicly funded international Human Genome Project (HGP).

24. While the systematic decoding was in progress, there was a race by several private sector firms to patent human genetic sequences. Claims were filed on some 127,000 human genes or partial gene sequences, confronting patent offices around the world with an impossible task and resulting in huge backlogs.

25. Patents on the human genome — including those on BRCA1 and BRCA2 — provide an extreme example of the lack of balance that can occur in our patent system. First, these are patents on *basic scientific knowledge* — the very instructions inside each of our cells that determine what proteins are produced. While all intellectual property rights circumscribe the use of knowledge or information, these patents are on the *information itself*- the isolated human gene sequence, for example. Knowledge is the most important input into knowledge. This is why, to get a patent, you have to disclose enough information that somebody can replicate what is being patented and build upon that knowledge. However, in the case of a genetic sequence, one cannot build upon the knowledge without having "access" to the genetic sequence. But any use of the sequence is barred by the patent. Furthermore, genes and their mutations are *natural phenomena,* not human inventions. The researchers and private companies that applied for these patents

did not invent this gene; they only identified what was already there.

26. The marginal social benefits of patenting genes clearly do not measure up to the profound costs. Since the publicly financed HGP has succeeded in decoding the entire human genome, there was really little value added by a race to decode a part of or even the whole genome. And the lock on knowledge resulting from the granting of these patents has served to impede follow-on research. In the case of Myriad Genetics' patents on BRCA1 and BRCA2, the value of Myriad's efforts was minimal: the knowledge of the precise sequence of the BRCA1 and BRCA2 genes was produced at best a little sooner than if not at the same time as it might have been otherwise. But the costs to society have been enormous. The high price that Myriad charges for its test (more than $3,000 for full sequencing) means that many women who could otherwise have been tested, discovered that they were at risk, and taken appropriate remediation might die instead. In addition, the patents have interfered with the ability of other labs to offer diagnostic testing and have discouraged the search for better screening tests.

27. Myriad and advocates of sustaining the BRCA patents claim that the high profitability of each test provides Myriad with an incentive to ensure that more people are tested and to ensure that such testing is covered by insurance. The flaws in this reasoning should be obvious. To be sure, a monopolist has a greater incentive to market and advertise his product, because of the large margin between price and marginal cost; yet the

overwhelming consensus within the economics profession is that, nonetheless, the social cost of monopoly is great. Higher prices resulting from monopoly power inevitably lead to lower utilization, especially on the part of those without full insurance. Currently, some 50 million residents in the United States do not have health insurance, and not all of those with health insurance — including some of the plaintiffs in this case — have full coverage for the costs of testing.[3] Given the high price of the tests, most of these will not be tested, and many of these may, as a result, not take appropriate actions which would have prevented their premature death.

28. The argument that because of its monopoly profits, Myriad has a greater incentive to promote testing is especially not persuasive, given the widespread awareness of breast cancer and the active role of the public and NGOs in promoting this awareness. Myriad's experts do not provide evidence that the extent of testing is greater in the United States, where the patent has been honored, than, say, in Ontario, Canada, where it has not been honored.

29. The argument that Myriad has succeeded in getting some insurance companies and third party payers to pick up the tab does not obviate the economic and social costs. Costs borne by the insurance company are shifted to the buyers of insurance; the higher costs lead to more uninsured. A

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[3] Complaint in *Association for Molecular Pathology et al. V. United States Patent and Trademark Office* et al., ¶ 93.

considerable portion of the costs are shifted to taxpayers. The higher health care costs mean that access to other services are curtailed. Budget stringency overall inevitably will mean that government research budgets will be cut, impeding the flow of basic research on which so much depends.

30. That there are high economic and social costs simply cannot be denied. The only question (from an economic perspective) is whether the benefits of the extension of patent protection in this area is worth the cost. The alleged benefit is increased innovation. In fact, this is one of the areas in which innovation may be impeded.

PATENT PROTECTION ON GENES IS NOT NECESSARY TO STIMULATE BIOMEDICAL RESEARCH BUT INSTEAD MAY HINDER FOLLOW-ON INNOVATION

31. Proponents of excessively strong IP rights argue that without IP protection there will be no research at all. This is clearly wrong: countries without IP rights — Switzerland had none until 1907, the Netherlands until 1912 — were highly innovative. IP is part — but only part — of a country's "innovation system."

32. Traditionally, IP has played little role in promoting basic science. Major breakthroughs — including understanding the genetic structure of life — have bubbled out of research universities and government-funded research laboratories. Traditionally, academia has believed in "open architecture," meaning that the knowledge that research produces should be made public to encourage innovation. The great scientists are driven

by an inner quest to understand the nature of the universe; the extrinsic reward that matters most to them is the recognition of their peers.

33. One of the reasons that basic research is advanced most by *not* resorting to intellectual property protection is that, while doing so would have questionable benefits, the costs are apparent. Universities thrive on a free flow of information, with each researcher quickly building on the work of others, typically even before it is published. If every time a researcher had an idea, he ran down to the patent office, he would spend more time there — or with his lawyers — than in his lab.

34. Many of the most important ideas of basic science and mathematics — mathematical theorems, for instance — cannot be patented, and rightly so: the cost in terms of discouraging follow-on innovation would be enormous, and the benefit would be small.

35. The sequencing of genes and the uncovering of disease-gene correlations are basic scientific research. Gene sequences are basic scientific knowledge. They are products of nature, not of invention. Genetic sequences are also laws of nature in that they dictate instructions for the building of proteins. As such, not only are patents on genes and gene-disease correlations unnecessary for stimulating research in genetics, but they also impede the dissemination of information, slowing further research and technological advancement.

36. Unlike in the area of drug development, expensive clinical trials are not necessary before a gene sequence can be used in the development of a molecular diagnostic test. Thus, patent protection is

not necessary for ensuring that genetic tests come to market. Instead, gene patents prevent others from developing and offering additional, alternative, and perhaps cheaper tests for individual or combinations of genes that have been patented.

37. The adverse impacts on innovation of the failure to grant this and other patents for genes is particularly questionable for two reasons. The first is that, by the mid-eighties, it was clear that it was simply a matter of time before the human genome would be decoded. The basic methodological research had already been done. Governments around the world had already committed the resources for the decoding. This is one of those instances where there was little benefit to the "patent race." Net, there was a social cost: while the discovery occurred a little earlier, the cost of lack of access discussed in the paragraphs above and the impediment to follow on research (discussed in ¶ 19) almost surely outweigh these slight benefits. Scarce research talent was diverted from areas where the social returns would have been far higher.

38. The Myriad and similar patents and the discovery that they entailed thus did not contribute to the store of knowledge, but they impeded innovation in several ways. I have discussed two of these: the reduction of public funds available for research and the diversion of scarce talent in the socially unproductive race to be first. But more significant perhaps is the impediment to follow-up research, which might, for instance, result in a lower cost or a more accurate test. This is especially so given the presence in this market of universities and government agencies interested in detection of the

risk of breast cancer, and willing to provide the benefits of the knowledge that they produce at the marginal cost of testing. Impediments to research hold even for basic research. An empirical analysis performed by Murray and Huang (2005) showed that patents on genes resulted in a 5%-17% decline in public knowledge generation (as measured by the annual rate of forward citations) as compared with genes that were simply published and not patented. This study additionally showed that the negative impact of a gene patent grant on follow-on publications was worse when the patent assignee was from the private sector, when the patent was especially broad in scope, and when the gene was closely linked to human disease.[4]

39. More generally, while the enclosure of the knowledge commons resulting from patents has adverse effects in limiting usage, it has also had perhaps more serious negative impacts on discouraging further innovation by insisting on expensive licenses or not allowing any usage of the scientific information at all. Williams (2009)[5] compares the subsequent scientific research and product development outcomes on genes sequenced

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[4] Kenneth G. Huang and Fiona E. Murray, "Does patent strategy shape the long-run supply of public knowledge? Evidence from human genetics," (September 1. 2008). *Academy of Management Journal*, Forthcoming. Available at SSRN: http://ssrn.com/abstract=1249522

Heidi Williams, Intellectual Property Rights and Innovation: Evidence from the Human Genome, unpublished, Dec. 30. 2009, available at:
http://vww.people.fas.harvard.edu/~hlwill/papers/Williams_jmp.pdf

by the private firm Celera and the public Human Genome Project. Her analysis suggests that Celera's intellectual property which enclosed knowledge led to a 30 percent reduction in subsequent scientific and product development outcomes.

40. Advocates of the Myriad and similar patents wish to shift the discussion from whether the patent system encourages or discourages innovation. That is not the issue. The issue is whether the particular category of patents under discussion does so, and does so to a sufficient extent to justify the large social costs of the restrictions on the use of knowledge and the extension of monopoly power. It is clear that the framers of the Constitution could not have had in mind the patenting of genes when they gave the Federal government the right to grant patents. So too, most of the Court decisions that have helped shape America's intellectual property regime could not have taken into account the fast evolution of America's complex innovation system. One of the factors that this Court will need to assess are the marginal social costs and benefits of the extension of patent coverage to genes, and the terms and conditions under which such coverage is extended. In my judgment, the overwhelming evidence is that the Myriad patents have brought few benefits, but significant social costs.

I declare, pursuant to 28 U.S.G. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Joseph E. Stiglitz

Joseph E. Stiglitz, Ph.D.

Executed on January 19, 2010

EXHIBIT 1

[EXHIBIT 1 OMITTED]

[Declaration of Fiona E. Murray, Ph.D., filed January 20, 2010] [Caption Omitted In Printing] [Exhibits 1-3 Omitted]

I, FIONA E. MURRAY, Ph.D., certify under penalty of perjury that the following is true and correct:

1. I am an Associate Professor of Management of Technological Innovation and Entrepreneurship at the Massachusetts Institute of Technology (MIT) as well as an Affiliated Professor in the Harvard-MIT Division of Health Science and Technology.

2. I submit this declaration in support of Plaintiffs in the above-captioned case.

3. I received both my Bachelor's and Master's degrees in Chemistry from the University of Oxford in 1989 and 1990, respectively. I received a Ph.D. in Applied Sciences from the Harvard University School of Engineering and Applied Sciences in 1996.

4. My research focuses on the study of science commercialization, the organization of scientific research and the role of science in national competitiveness. I have studied how growing economic incentives, particularly intellectual property (IP), influence the rate and direction of scientific progress, particularly in the areas of genomics, stem cells and mouse genetics. I have authored and published articles on my research in numerous journals including *Science*, the *New England Journal of Medicine*, *Nature Biotechnology*, *Research Policy*, *Organization Science* and the *Journal of Economic Behavior & Organization*. A complete list of my professional credentials and

publications is contained in my curriculum vitae, attached as Exhibit 1.

5. In 2005, I was awarded a grant to research the impact of gene patenting on scientific progress and commercialization. My empirical research in this area demonstrates that gene patents -more precisely patents that claim human protein-encoding nucleotide sequences- decrease the long-run production of public genetic knowledge as measured by citations to related gene publications. This general trend is exacerbated in situations when patents are broad in scope, privately owned, or where the patented genes are closely linked to human disease, and especially cancer. All of these conditions are relevant to the patents held by Myriad Genetics that are the subject of this case.

GENE PATENT LANDSCAPE

6. Gene patents have been the subject of considerable debate for many years. In 2005, to provide more empirical data on this topic, my colleague Kyle Jensen and I published an article in *Science* documenting the patent landscape of the human genome. Using a precise algorithm based on bioinformatics methods, we identified *all* patents that claimed human nucleotide sequences (as listed using the REFSEQ language) in the claims and physically mapped the gene-oriented IP rights to specific locations along the human genome. Our results revealed that **4382** of the **23,688** genes listed in the National Center for Biotechnology Information's gene database, or nearly **20% of human genes**, are explicitly claimed (for some use or another) as United States intellectual property.

The article in which these results were published is attached as Exhibit 2.

EFFECTS OF GENE PATENTS ON LONG-RUN SUPPLY OF PUBLIC KNOWLEDGE

7. Building on the results of the 2005 paper, my colleague Kenneth Huang and I devised a study to gauge the influence of gene patenting on the long-run supply of public knowledge. Our starting point for this analysis was to identify and examine human gene patent-paper pairs. These are cases where a gene sequence is disclosed both in the claims of a gene patent and also discussed in a related publication by a related set of authors..

8. In accordance with U.S. patent law, a purported inventor who wishes to patent an invention must file a patent application no later than one year after publishing the invention. The patent application process often takes over two years. Consequently, in cases of gene patent-paper pairs, there is typically a three- to four-year lag between the publication of a paper on a gene sequence and the issuance of a patent disclosing the sequence of that gene.

9. During this lag period of three or four years, the not-yet-patented information is essentially part of the public knowledge stream. Follow-on researchers are entitled to treat the information as such. This means the follow-on researcher who relies upon the information typically is obligated to do no more than acknowledge the original author with a citation in any follow-on work. In other words, in the period prior to the patent grant, genetic knowledge is disclosed in a paper and contributions to future

public knowledge stream building on that paper accumulate in an institutional setting characterized by public norms and practices.

10. Once a patent is granted, the patent owner may legally provide, restrict, or prohibit access to any researcher seeking to build upon the patentee's contribution. Any follow-on accumulation of knowledge takes place in the shadow of formal legal private property.

11. By comparing the difference in gene patent paper citations in the pre- and post-grant period for those affected by the patent grant to the same difference for unaffected gene paper citations, we can evaluate the precise impact of the change.

12. From the human gene patents identified in the 2005 patent landscape documentation, my colleague and I identified 1279 patent-paper pairs: instances in which a gene sequence was disclosed in both the publication and claims of the gene patent. The 1279 pairs we analyzed disclose 2637 human gene sequences in publications and correspond to 11 % of the known human genes as defined by NCBI. We then studied follow-on research published during both the pre- and post-patent grant periods for each gene patent-paper pair – as captured by publication citations.

13. We hypothesized that the grant of a gene patent would negatively impact the rate of follow-on publications.

14. We also hypothesized the degree to which a gene patent would negatively impact the rate of follow-on publication would depend upon a number of factors, including: 1) the breadth of the patent

granted over the knowledge claimed; 2) whether the patent is assigned to a private sector compared to the public sector; and 3) the applicability of the knowledge claimed (the more useful the knowledge associated with the patent — for example, where the gene sequence is directly correlated with a common disease – the more the patent would deter follow-on publications.)

15. We took an empirical approach to testing these hypotheses. We used publication citations to each gene paper (i.e. peer-reviewed publications citing the focal paper) as a proxy for follow-on public knowledge accumulation. The full details of our methodology and variables used in our analysis are disclosed in our publication of the study, attached as Exhibit 3.

KEY RESULTS

16. The study results supported our hypothesis. We found that the negative impact of patent grant on the future public knowledge production, as measured by the annual rate of forward citations to the paired paper, was 17%. A more stringent interpretation of the results showed a 5% decline in the expected rate of citations. This more stringent interpretation suggests that follow-on genetic researchers forego about one in ten research projects (or more precisely research publications) because of the causal impact of the gene patent grant.

17. Our results additionally showed that the negative impact of a gene patent grant on follow-on publications was worse when the patent assignee was from the private sector compared to the public sector (a 6%-9% decline as compared with 0%-3% for academic patents).

18. Our results also showed that patent scope and strength had a modest, but statistically significant, impact on the degree to which a gene patent grant had a negative impact on follow-on publications.

19. Our results additionally showed that the negative effect of patents on follow-on public knowledge production is greatest for genes closely linked to human diseases. While we would expect that gene papers on disease-related genes would be more highly cited, our methodology allowed us to distinguish between this "levels" effect and the effect of a gene patents grant on annual citations. Only disease genes listed in the Online Mendelian Inheritance in Man (OMIM) database were found to have a significant 8% reduction in forward citations. In looking only at cancer genes, the effect was even more pronounced: the sample of proven cancer genes sees a negative impact of 11% as compared with 4% in the non-cancer sample.

CONCLUSION

20. Based on my expertise in studying the effects of gene patents on the stream of public knowledge and in particular on the results of the 2009 empirical study described above, it is my opinion that the Myriad patents at issue in the instant lawsuit are likely to have negatively impacted the accumulation of public knowledge of the BRCA1 and BRCA2 genes by between 5 and 10%. The negative impact of the patents at issue is exacerbated by the fact that Myriad Genetics is an assignee from the private sector, the patents in question are exceedingly broad, and the genes at issue are cancer genes.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

/s/ Fiona E. Murray

Fiona E. Murray

Executed on January 19, 2010

EXHIBITS 1-3

[EXHIBITS 1-3 OMITTED]

[Supplemental Declaration of Harry Ostrer, filed September 14, 2011] [Caption Omitted In Printing]

1. I am Harry Ostrer, M.D., one of the plaintiffs/appellees in this case. I submitted a prior declaration in this case. A1462-1504. The Court's opinion on this appeal contains a discussion of my standing. Opinion at 19-21, 27-35.

2. Defendant/appellant Myriad has filed a Petition for Panel Rehearing in which they argue that the case is moot as a result of my actions. I am submitting this declaration in opposition to the Petition.

3. At the time of the appeal in this case, I was employed at New York University Langone Medical Center (NYU). A1463-64. Effective August 29, 2011, I changed jobs. As of that date, I am a Professor of Pathology and Genetics at the Albert Einstein College of Medicine and Montefiore Medical Center. I am also Director of Genetic and Genomic Diagnostics at Montefiore Medical Center in New York.

4. At the Human Genetics Program and Molecular Genetics Laboratory at NYU, "that I direct[ed], my staff and I engage[d] in both research and clinical practice relating to genetic related susceptibility to disease." A 1464. As Director of Genetics and Genomic Diagnostics at Montefiore Medical Center, which I direct, my staff and I engage in both research and clinical practice relating to genetically related susceptibility to disease.

5. At NYU, "I ha[d] the capability and desire" to "provide patients with the results of BRCAl/2 related genetic screening for the susceptibility to breast

cancern. A 1464. I have the same capability and desire at Montefiore.

6. At NYU, I was prevented from doing so "as a result of Myriad's assertion of its patents." A 1464. At Montefiore, I am prevented from doing so as a result of Myriad's assertion of its patents.

7. While at NYU, I declared that "[i]f the patents were invalidated, I would immediately take steps to begin clinical sequencing of the BRCAl and BRCA2 genes." A 1466. At Montefiore, if the patents were invalidated, I would immediately take steps to begin clinical sequencing of the BRCA1 and BRCA2 genes.

8. At NYU, I had "all of the personnel, expertise, and facilities necessary to do various types of sequencing of the BRCA1 and BRCA2 genes and I [had] the strong desire for my lab to provide such sequencing services." A 1466. At Montefiore, I have all of the personnel, expertise and facilities necessary to do various types of sequencing of the BRCA1 and BRCA2 genes and I have the strong desire for my lab to provide such sequencing services.

9. All of the rest of the facts contained in my prior declaration remain true. I would tell research subjects of the results of their tests, I would support and be able to provide an alternate source for testing, I would learn more about variants of uncertain significance and share those results with the scientific community. A1467-69.

10. In short, using the language from this Court's opinion, I still "seek[] to undertake BRCA diagnostic testing." In addition, in my new position, I have "the resources and expertise to immediately undertake clinical BRCA testing." Finally, I "will immediately

begin such testing" if the patents in this case are invalidated.

11. I remain deterred from doing so because I was personally threatened by Myriad. A 1494. As a result of that letter, I remain convinced that if I were to engage in BRCA clinical testing, Myriad would sue me for infringement. I will also not begin such testing because I remain aware that Myriad has asserted its patent rights against similarly situated parties.

12. I am aware that Myriad has argued that the letter I received should be considered as directed solely at NYU and its employees and not at me. I cannot reconcile that argument with the fact that the letter was addressed to me by name. It is inconceivable to me that I could have moved to a different job, engaged in the exact same activity, and been certain that Myriad would take no action. I felt personally threatened then and I continue to feel so today.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true a correct to the best of my knowledge and belief.

/s/ Harry Ostrer

Harry Ostrer, M.D.

Executed on September 12, 2011

[Declaration of Richard Marsh, filed May 30, 2012] [Caption Omitted In Printing]

I, Richard Marsh, hereby declare that:

1. I am Executive Vice President, General Counsel, and Secretary at Myriad Genetics, Inc., one of the appellants in this case. I have served in these positions since November 2002. My responsibilities include, among other things, offering licenses to, and negotiating with, other parties with respect to Myriad's intellectual property.

2. I am aware that, on May 21, 1998, Myriad sent a letter addressed to Dr. Harry Ostrer in his professional capacity as the Director of New York University's Molecular Genetics Laboratory ("NYU"). In that letter, Myriad offered a license to NYU and enclosed a draft collaboration agreement between Myriad and NYU. (A2964-74.) The offer of license was not to Dr. Ostrer.

3. I understand that, effective August 29, 2011, Dr. Ostrer no longer works at NYU, and that, on or around that date, he became employed instead at Montefiore Medical Center and the Albert Einstein College of Medicine (collectively, "Montefiore").

4. Myriad has never sent a letter or otherwise communicated with Montefiore regarding any of Myriad's patents, including the patents at issue in this litigation.

5. Myriad has never offered a license or other collaboration agreement to Montefiore.

6. Myriad is not aware of any present or planned actions by Montefiore that would interfere with Myriad's rights under the patents at issue in this

litigation. By way of example, Myriad is not aware of any BRCA clinical genetic testing currently performed by Montefiore, nor is Myriad aware of whether Montefiore possesses the necessary authorizations—such as CLIA certification (under the Clinical Laboratory Improvement Amendments) or New York State certification—to perform such testing for individual patient diagnoses, or, if uncertified, how long it would take Montefiore to obtain those authorizations. In short, because Myriad is completely unaware of what (if any) activities have been (or are presently being) undertaken by Montefiore's facilities, let alone what activities Dr. Ostrer or any other scientist affiliated with Montefiore have engaged in or are engaging in, Myriad does not have any dispute with Montefiore or any of its personnel, and never has.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct.

/s/ Richard Marsh
Richard Marsh

Executed on: May 25, 2012

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Supreme Court, U.S.
FILED

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OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

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THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,

Petitioners,

—v.—

MYRIAD GENETICS, INC., ET AL.,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES
COURT OF APPEALS FOR THE FEDERAL CIRCUIT

JOINT APPENDIX
VOLUME II OF II

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PETITION FOR WRIT OF CERTIORARI FILED SEPTEMBER 25, 2012
PETITION FOR WRIT OF CERTIORARI GRANTED NOVEMBER 30, 2012

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US005747282A

United States Patent [19]

Skolnick et al.

[11] **Patent Number:** 5,747,282

[45] **Date of Patent:** May 5, 1998

[54] **17Q-LINKED BREAST AND OVARIAN CANCER SUSCEPTIBILITY GENE**

[75] Inventors: **Mark H. Skolnick**; **David E. Goldgar**; **Yoshio Miki**; **Jeff Swensen**; **Alexander Kamb**; **Keith D. Harshman**; **Donna M. Shattuck-Eidens**; **Sean V. Tavtigian**, all of Salt Lake City, Utah; **Roger W. Wiseman**; **P. Andrew Futreal**, both of Durham, N.C.

[73] Assignees: **Myriad Genetics, Inc.**; **University of Utah Research Foundation**, both of Salt Lake City, Utah; **The United States of America as represented by the Secretary of Health and Human Services**, Washington, D.C.

[21] Appl. No.: **483,554**

[22] Filed: **Jun. 7, 1995**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 409,305, Mar. 24, 1995, abandoned, which is a continuation-in-part of Ser. No. 348,824, Nov. 29, 1994, abandoned, which is a continuation-in-part of Ser. No. 308,104, Sep. 16, 1994, which is a continuation-in-part of Ser. No. 300,266, Sep. 2, 1994, abandoned, which is a continuation-in-part of Ser. No. 289,221, Aug. 12, 1994, abandoned.

[51] Int. Cl.^{6} **C12P 21/06**; C12Q 1/68; C07H 21/04

[52] U.S. Cl. **435/69.1**; 435/6; 435/320.1; 435/325; 536/23.5; 536/24.31; 536/24.33; 935/9; 935/60; 935/66

[58] **Field of Search** 536/23.1, 23.5, 536/24.33; 435/69.1, 6, 7.1, 91.1, 91.2, 375, 320.1; 514/44

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Primary Examiner—Bruce R. Campell

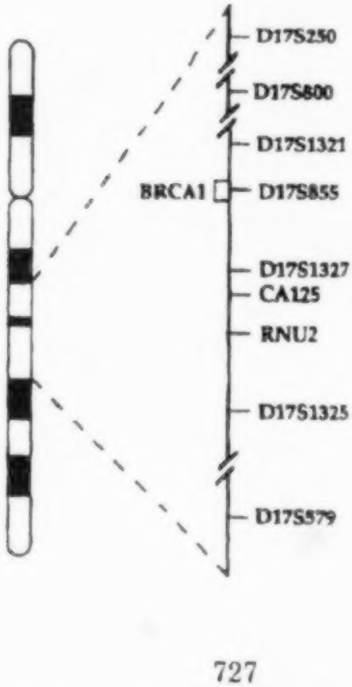
Assistant Examiner—Abdur Razzaque

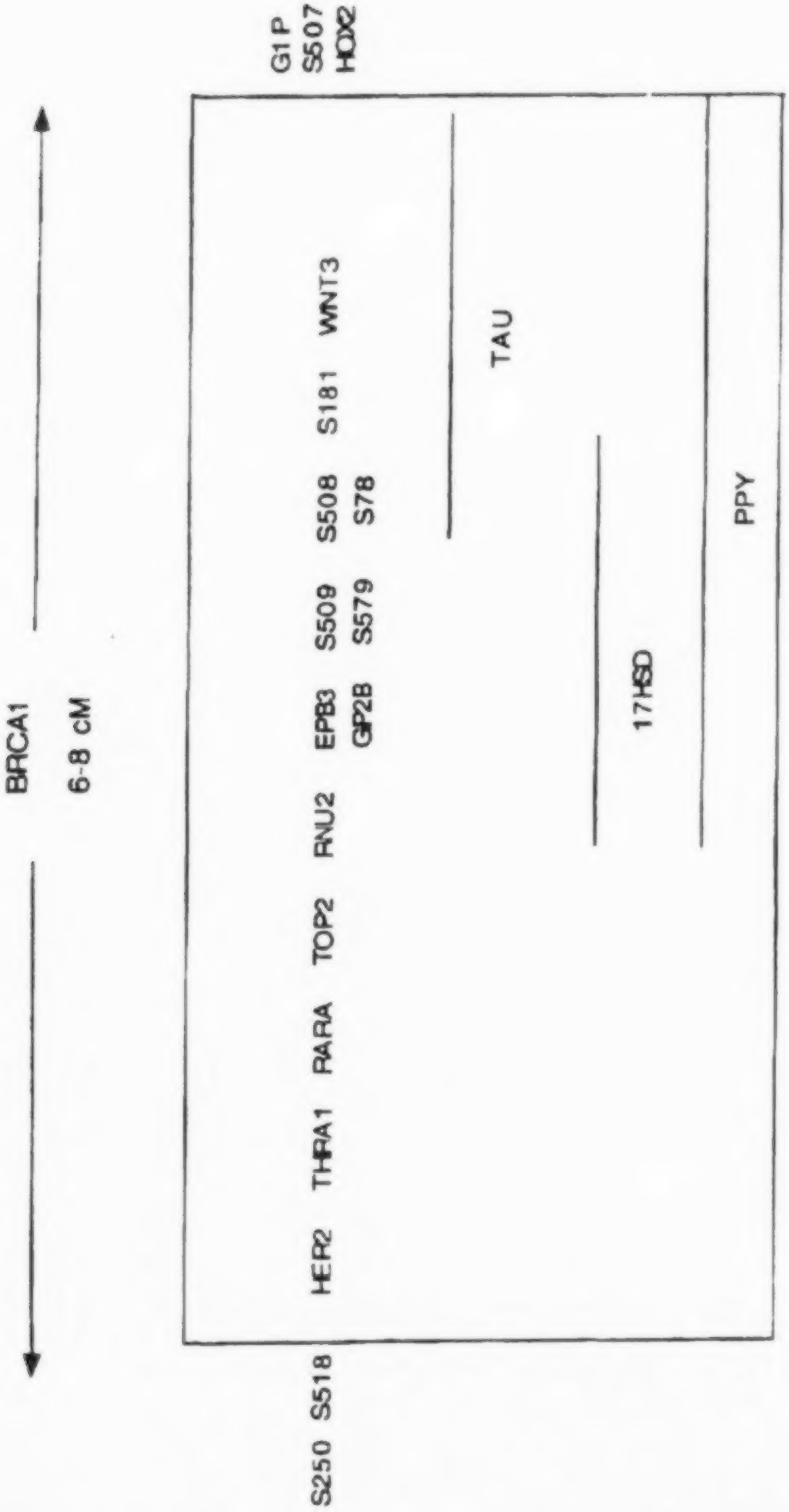
Attorney, Agent, or Firm—Venable, Baetjer, Howard & Civiletti, LLP

[57] **ABSTRACT**

The present invention relates generally to the field of human genetics. Specifically, the present invention relates to methods and materials used to isolate and detect a human breast and ovarian cancer predisposing gene (BRCA1), some mutant alleles of which cause susceptibility to cancer, in particular breast and ovarian cancer. More specifically, the invention relates to germline mutations in the BRCA1 gene and their use in the diagnosis of predisposition to breast and ovarian cancer. The present invention further relates to somatic mutations in the BRCA1 gene in human breast and ovarian cancer and their use in the diagnosis and prognosis of human breast and ovarian cancer. Additionally, the invention relates to somatic mutations in the BRCA1 gene in other human cancers and their use in the diagnosis and prognosis of human cancers. The invention also relates to the therapy of human cancers which have a mutation in the BRCA1 gene, including gene therapy, protein replacement therapy and protein mimetics. The invention further relates to the screening of drugs for cancer therapy. Finally, the invention relates to the screening of the BRCA1 gene for mutations, which are useful for diagnosing the predisposition to breast and ovarian cancer.

20 Claims, 18 Drawing Sheets

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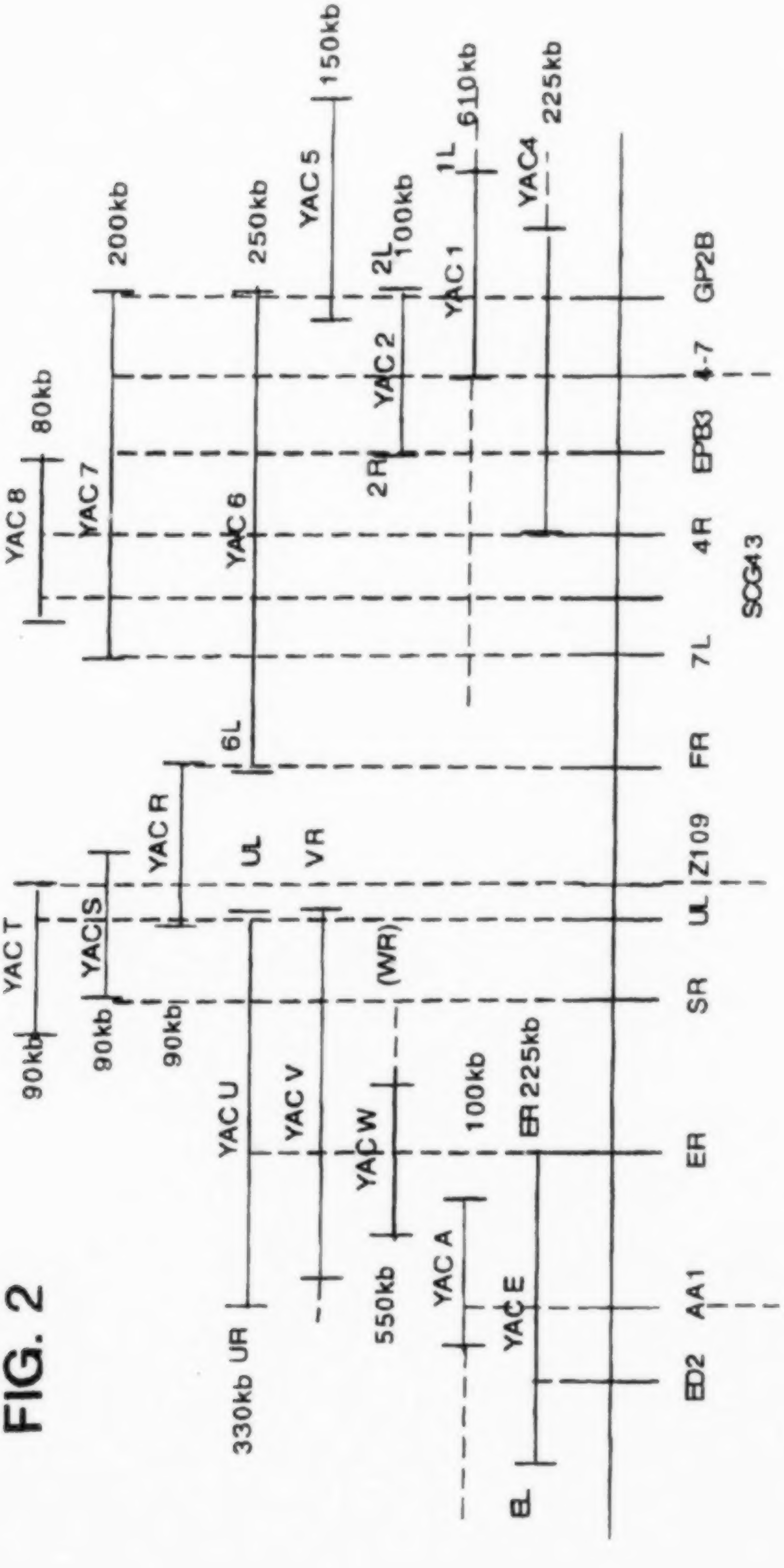
Map of the early onset breast and ovarian cancer region (BRCA1)

FIG. 1

FIG. 2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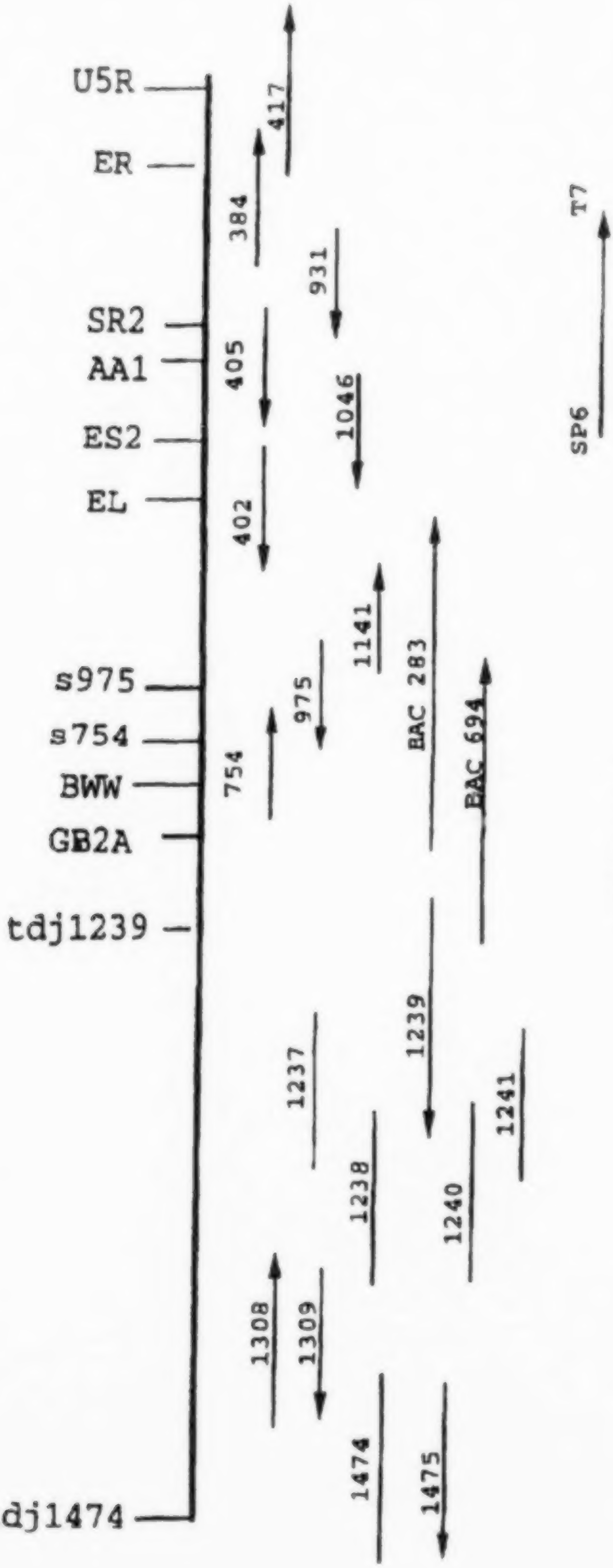
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SP6
1237
1239
1238
1241
1240
1308
1309
1474
1475

FIG. 3

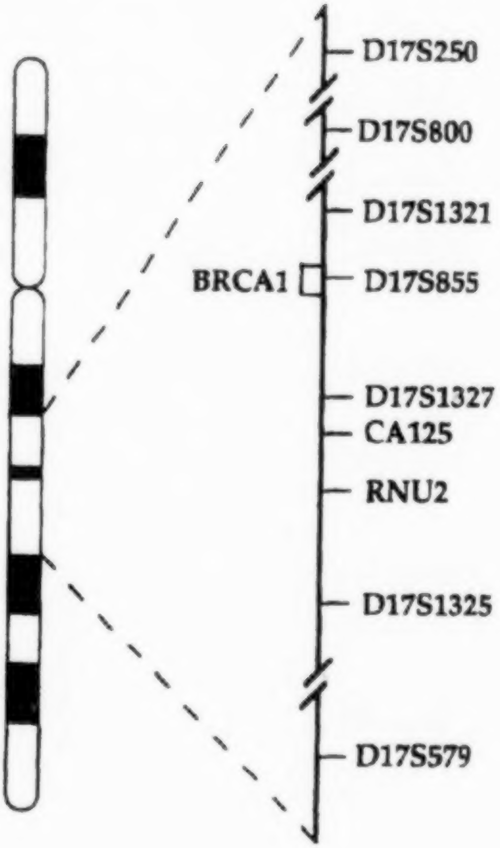
D17S250
D17S800
D17S1321
BRCA1
D17S855
D17S1327
CA125
RNU2
D17S1325
D17S579

FIG. 4

SEQ. ID NO:		
82	BRCA1	CPICLELIKEPVSTK-CDHIFCKFCMLKLLNQKK---GPSQCPLCK
83	RPT1	CPICLELLKEPVSAD-CNHSFCRACITLNYESNRNTDGKGNCPVCR
84	RIN1	CPICLDMLKNTMTTKECLHRFCSDCIVTALRS-----GNKECPTCR
85	RFP1	CPVCLQYFAEPMMLD-CGHNICCACLARCWGTAC---TNVSCPQCR
	C3HC4 motif	C--C------------C-H--C--C----------------C--C

FIG. 5

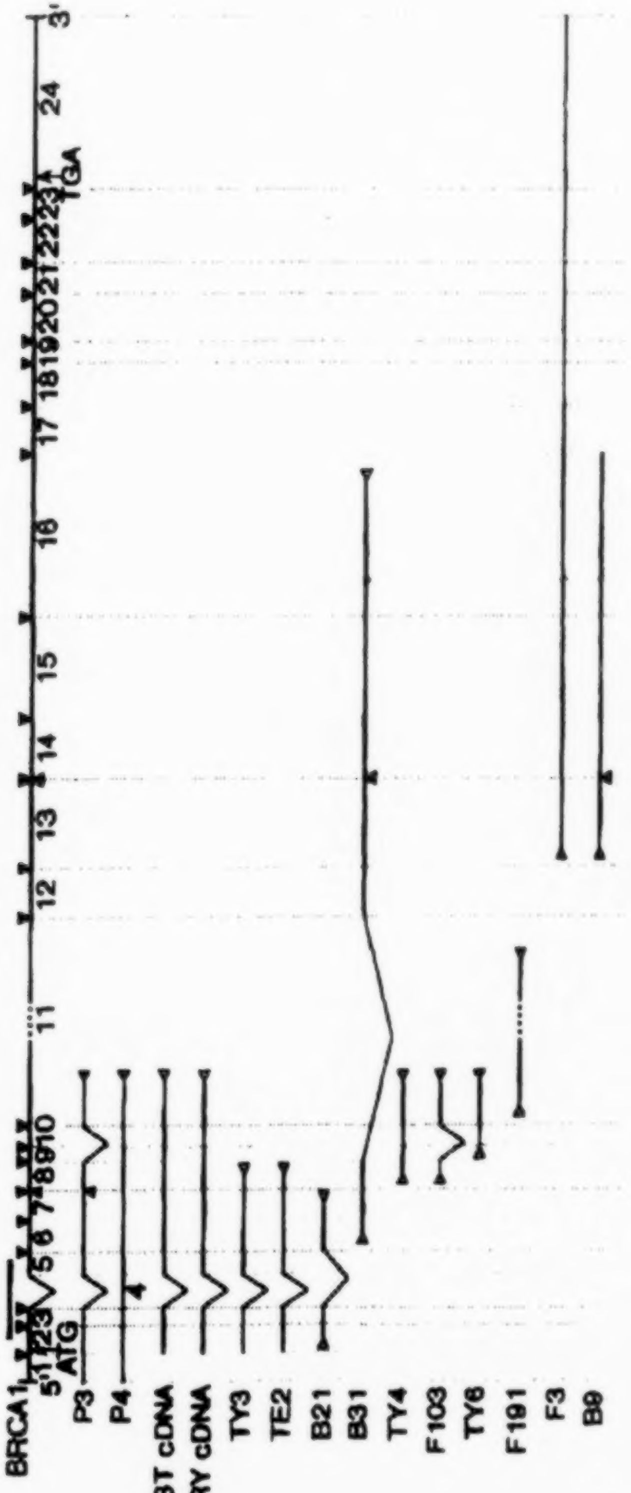
BRCA1
5'
1
2
3
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
3'
ATG
TGA
P3
P4
BREAST cDNA
OVARY cDNA
TY3
TE2
B21
B31
TY4
F103
TY6
F191
F3
B9

FIG. 6

Breast
Leukocyte
Colon
Small Intestine
Ovary
Testis
Prostate
Thymus
Spleen
9.50
7.50
4.40
9.50
7.50
4.40
2.40

FIG. 7

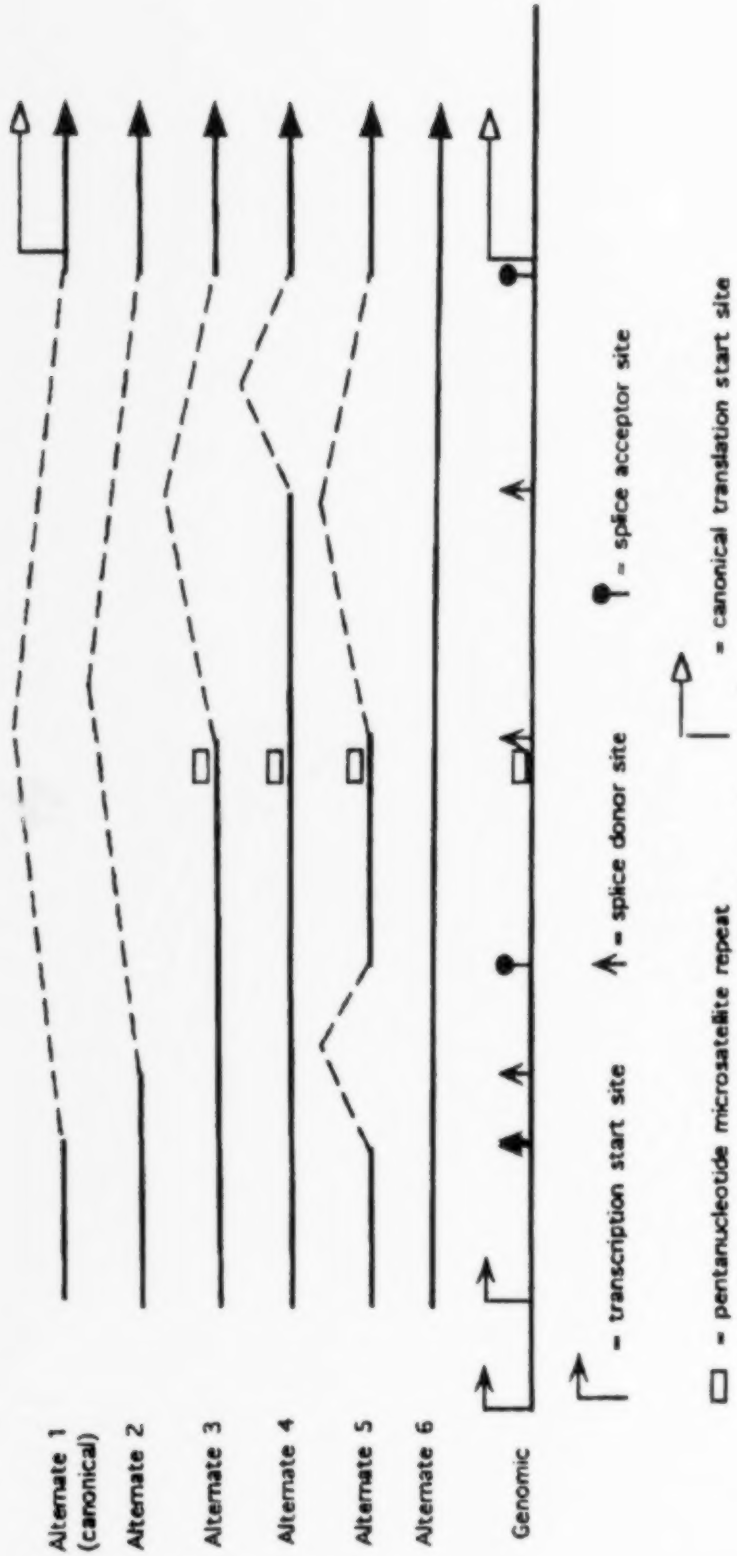
Alternate 1
(canonical)
Alternate 2
Alternate 3
Alternate 4
Alternate 5
Alternate 6
Genomic
- transcription start site
- splice donor site
- splice acceptor site
- canonical translation start site
- pentanucleotide microsatellite repeat

FIG. 8

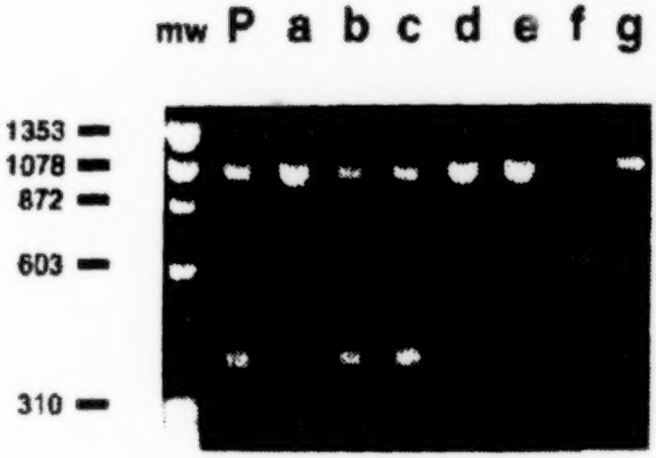
mw
P
a
b
c
d
e
f
g
1353
1078
872
603
310

FIG. 9A

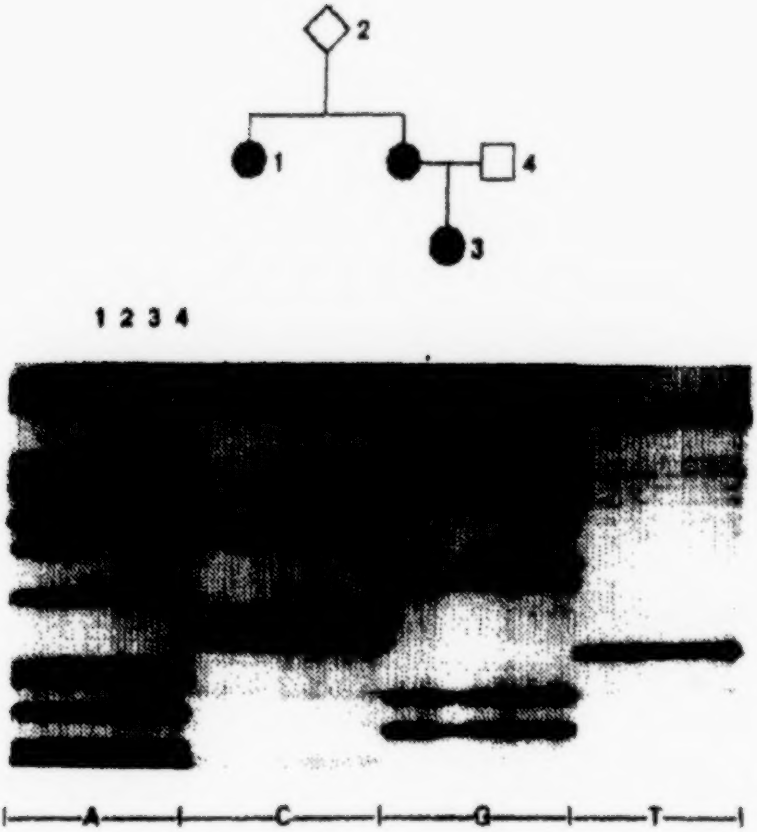
2
1
4
3
1 2 3 4
A
C
G
T

FIG. 9B

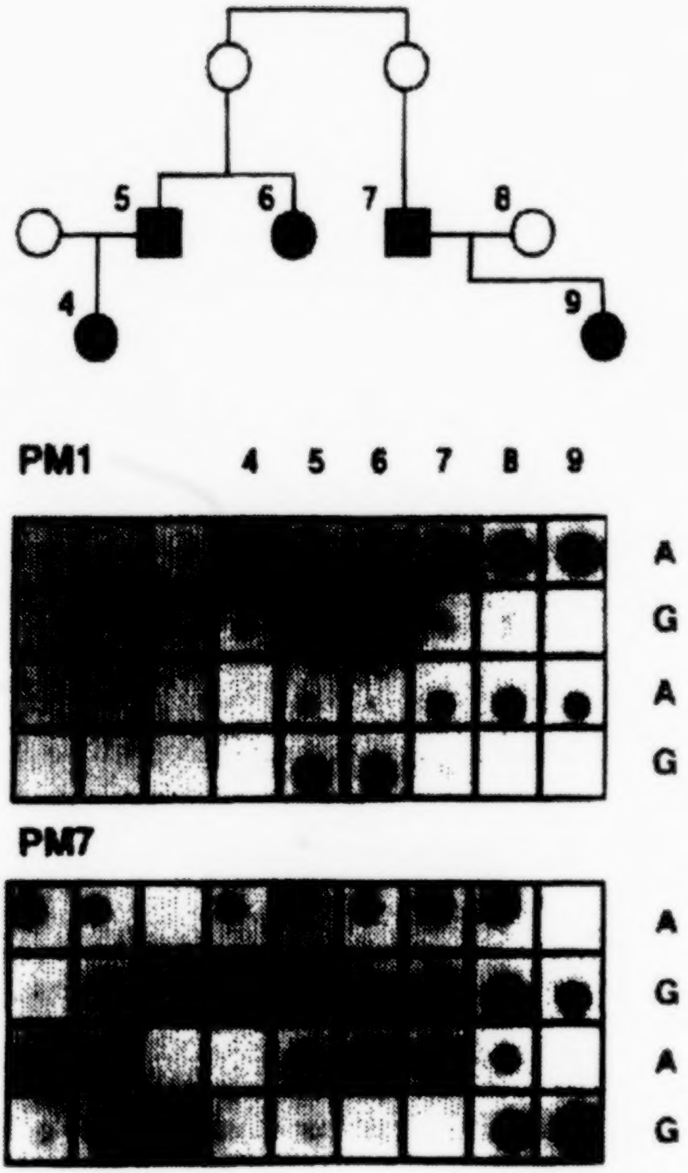
5
6
7
8
4
9
PM1
4 5 6 7 8 9
A
G
A
G
PM7
A
G
A
G

FIG. 9C

```
   1  gaggctagagggcaggcactttatggcaaactcaggtagaattcttcctcttccgtctct
  61  ttccttttacgtcatcggggagactgggtggcaatcgcagcccgagagacgcatggctct
 121  ttctgccctccatcctctgatgtaccttgatttcgtattctgagaggctgctgcttagcg
 181  gtagccccttggtttccgtggcaacggaaaagcgcgggaattacagataaattaaaactg
 241  cgactgcgcggcgtgAGCTCGCTGAGACTTCCTGGACCCCGCACCAGGCTGTGGGGTTTC
 301  TCAGATAACTGGGCCCCTGCGCTCAGGAGGCCTTCACCCTCTGCTCTGGGTAAAGgtagt
 361  agagtcccgggaaagggacagggggcccaagtgatgctctggggtactggcgtgggagag
 421  tggatttccgaagctgacagatgggtattctttgacgggggtaggggcggaacctgaga
 481  ggcgtaaggcgttgtgaaccctggggagggggcagtttgtaggtcgcgagggaagcgct
 541  gaggatcaggaagggggcactgagtgtccgtgggggaatcctcgtgataggaactggaat
 601  atgccttgagggggacactatgtctttaaaaacgtcggctggtcatgaggtcaggagttc
 661  cagaccagcctgaccaacgtggtgaaactccgtctctactaaaaatacnaaaattagccg
 721  ggcgtggtgccgctccagctactcaggaggctgaggcaggagaatcgctagaacccgga
 781  ggcggaggttgcagtgagccgagatcgcgccattgcactccagcctgggcgacagagcga
 841  gactgtctcaaaacaaaacaaaacaaaacaaaacaaaaaacaccggctggtatgtatgag
 901  aggatgggaccttgtggaagaagaggtgccaggaatatgtctgggaaggggaggagacag
 961  gatttgtgggagggagaacttaagaactggatccatttgcgccattgagaaagcgcaag
1021  agggaagtagaggagcgtcagtagtaacagatgctgccggcagggatgtgcttgaggagg
1081  atccagagatgagagcaggtcactgggaaaggttaggggcggggaggccttgattggtgt
1141  tggtttggtcgttgttgattttggttttatgcaagaaaaagaaaacaaccagaaacattg
1201  gagaaagctaaggctaccaccacctacccggtcagtcactcctctgtagctttctctttc
1261  ttggagaaaggaaaagacccaaggggttggcagcgatatgtgaaaaaattcagaatttat
1321  gttgtctaattacaaaaagcaacttctagaatctttaaaaataaaggacgttgtcattag
1381  ttcttctggtttgtattattctaaaccttccaaatcttcaaatttactttattttaaaa
1441  tgataaaatgaagttgtcattttataaacctttaaaaagatatatatatatgtttttct
1501  aatgtgttaaagTTCATTGGAACAGAAAGAAATGGATTTATCTGCTCTTCGCGTTGAAGA
1561  AGTACAAAATGTCATTAATGCTATGCAGAAAATCTTAGAGTGTCCCATCTGgtaagtcag
1621  caaaagagtgtattaatttgggattcctatgattatctcctatgcaaatgaacagaattg
1681  accttacatactagggaagaaaagacatgtctagtaagattaggctattgtaattgctga
1741  ttttcttaactgaagaactttaaaaatatagaaaatgattccttgttctccatccactct
1801  gcctctcccactcctctccttttcaacacaatcctgtggtccgggaaagacagggctctg
1861  tcttgattggttctgcactgggcaggatctgttagatactgcatttgctttctccagctc
1921  taaavvvvvvvvvvvvvvaaatgctgatgatagtatagagtattgaaggatcaatataat
1981  tctgttttgatatctgaaagctcactgaaggtaaggatcgtattctctgctgtattctca
2041  gttcctgacacagcagacatttaataaatattgaacgaacttgaggccttatgttgactc
2101  agtcataacagctcaaagttgaacttattcactaagaatagctttatttttaaataaatt
2161  attgagcctcatttattttctttttctcccccccctaccctgctagTCTGGAGTTGATCA
2221  AGGAACCTGTCTCCACAAAGTGTGACCACATATTTTGCAAgtaagtttgaatgtgttatg
2281  tggctccattattagcttttgtttttgtccttcataacccaggaaacacctaactttata
2341  gaagctttactttcttcaattaagtgagaacgaaaatccaactccatttcattctttctc
2401  agagagtatatagttatcaaaagttggttgtaatcatagttcctggtaaagttttgacat
2461  atattatctttttttttttttgagacaagtctcgctctgtcgcccaggctggagtgcagt
2521  ggcatgaggcttgctcactgcacctccgcccccgagttcagcgactctvvvvvvvvvvvv
2581  vtgagatctagaccacatggtcaaagagatagaatgtgagcaataaatgaaccttaaatt
2641  tttcaacagctactttttttttttttttttgagacagGGKCTTACTCTGTTGTCCCAGCT
2701  GGAGTACAGWGTGCGATCATGAGGCTTACTGTTGCTTGACTCCTAGGCTCAAGCGATCCT
2761  ATCACCTCAGTCTCCAAGTAGCTGGACTgtaagtgcacaccaccatatccagctaaattt
2821  tgtgttttctgtagagacggggtttcgccatgtttcccaggctggtcttgaactttgggc
2881  ttaacccgtctgcccacctaggcatcccaaagtgctaggattacaggtgtgagtcatcat
2941  gcctggccagtattttagttagctctgtcttttcaagtcatatacaagttcattttcttt
3001  taagtttagttaacaaccttatatcatgtattcttttctagcataaagaaagattcgagg
```

FIG. 10A

```
3061  ccvvvvvvvvvvvvvtgtgatcataacagtaagccatatgcatgtaagttcagttttcat
3121  agatcattgcttatgtagtttaggtttttgcttatgcagcatccaaaaacaattaggaaa
3181  ctattgcttgtaattcacctgccattactttttaaatggctcttaagggcagttgtgaga
3241  ttatcttttcatggctatttgcctttgagtattctttctacaaaaggaagtaaattaaa
3301  ttgttctttctttctttataatttatagATTTTGCATGCTGAAACTTCTCAACCAGAAGA
3361  AAGGGCCTTCACAGTGTCCTTTATGTAAGAATGATATAACCAAAAGgtatataatttggt
3421  aatgatgctaggttggaagcaaccacagtaggaaaaagtagaaattatttaataacatag
3481  cgttcctataaaaccattcatcagaaaaatttataaaagagttttagcacacagtaaat
3541  tatttccaaagttattttcctgaaagttttatgggcatctgccttatacaggtattgvvv
3601  vvvvvvvvvvvggtaggcttaaatgaatgacaaaaagttactaaatcactgccatcacacg
3661  gtttatacagatgtcaatgatgtattgattatagaggttttctactgttgctgcatctta
3721  tttttatttgtttacatgtcttttcttatttagtgtccttaaaaggttgataatcactt
3781  gctgagtgtgtttctcaaacaatttaatttcagGAGCCTACAAGAAAGTACGAGATTTAG
3841  TCAACTTGTTGAAGAGCTATTGAAAATCATTTGTGCTTTTCAGCTTGACACAGGTTTGGA
3901  GTgtaagtgttgaatatcccaagaatgacactcaagtgctgtccatgaaaactcaggaag
3961  tttgcacaattactttctatgacgtggtgataagaccttttagtctaggttaattttagt
4021  tctgtatctgtaatctattttaaaaaattactcccactggtctcacaccttatttvvvvv
4081  vvvvvvvvaaaaaatcacaggtaaccttaatgcattgtcttaacacaacaaagagcatac
4141  atagggtttctcttggtttctttgattataattcatacatttttctctaactgcaaacat
4201  aatgttttcccttgtattttacagATGCAAACAGCTATAATTTTGCAAAAAAGGAAAATA
4261  ACTCTCCTGAACATCTAAAAGATGAAGTTTCTATCATCCAAAGTATGGGCTACAGAAACC
4321  GTGCCAAAAGACTTCTACAGAGTGAACCCGAAAATCCTTCCTTGgtaaaaccatttgttt
4381  tcttcttcttcttcttcttctttttcttttttttttcttttttttttttgagatggagtctt
4441  gctctgtggcccaggctagaagcagtcctcctgccttagccnccttagtagctgggatta
4501  caggcacgcgcaccatgccaggctaatttttgtatttttagtagagacggggtttcatca
4561  tgttggccaggctggtctcgaactcctaacctcaggtgatcvvvvvvvvvvvvvatgatg
4621  gagatcttaaaaagtaatcattctggggctgggcgtagtagcttgcacctgtaatcccag
4681  cacttcgggaggctgaggcaggcagataatttgaggtcaggagtttgagaccagcctggc
4741  caacatggtgaaacccatctctactaaaaatacaaaaattagctgggtgtggtggcacgt
4801  acctgtaatcccagctactcgggaggcggaggcacaagaattgcttgaacctaggacgcg
4861  gaggttgcagcgagccaagatcgcgccactgcactccagcctgggccgtagagtgagact
4921  ctgtctcaaaaaagaaaaaaaagtaattgttctagctgggcgcagtggctcttgcctgta
4981  atcccagcactttgggaggccaaggcgggtggatctcgagtcctagagttcaagaccagc
5041  ctaggcaatgtggtgaaaccccatcgctacaaaaaatacaaaaattagccaggcatggtg
5101  gcgtgcgcatgtagtcccagctccttgggaggctgaggtgggaggatcacttgaacccag
5161  gagacagaggttgcagtgaaccgagatcacgccaccacgctccagcctgggcaacagaac
5221  aagactctgtctaaaaaaatacaaataaaataaaagtagttctcacagtaccagcattca
5281  tttttcaaaagatatagagctaaaaaggaaggaaaaaaaaaagtaatgttgggcttttaaa
5341  tactcgttcctatactaaatgttcttaggagtgctggggttttattgtcatcatttatcc
5401  tttttaaaaatgttattggccaggcacggtggctcatggctgtaatcccagcactttggg
5461  aggccgaggcaggcagatcacctgaggtcaggagtgtgagaccagcctggccaacatggc
5521  gaaacctgtctctactaaaaatacaaaaattaactaggcgtggtggtgtacgcctgtagt
5581  cccagctactcgggaggctgaggcaggagaatcaactgaaccagggaggtggaggttgca
5641  gtgtgccgagatcacgccactgcactctagcctggcaacagagcaagattctgtctcaaa
5701  aaaaaaaaacatatatacacatatatcccaaagtgctgggattacatatatatatatata
5761  tatatattatatatatatatatatatatgtgatatatatgtgatatatatataacata
5821  tatatatgtaatatatatgtgatatatatataatatatatatgtaatatatatgtgatat
5881  atatatatacacacacacacacatatatatgtatgtgtgtgtacacacacacacacaaat
5941  tagccaggcatagttgcacacgcttggtagacccagctactcaggaggctgagggaggag
6001  aatctcttgaacttaggaggcggaggttgcagtgagctgagattgcgccactgcactcca
6061  gcctgggtgacagagcaggactctgtacacccccccaaaacaaaaaaaaaaagttatcagat
```

FIG. 10B

```
6121  gtgattggaatgtatatcaagtatcagcttcaaaatatgctatattaatacttcaaaaat
6181  tacacaaataatacataatcaggtttgaaaaatttaagacaacmsaaraaaaaawycmaa
6241  tcacamatatcccacacattttattattmctmctmcwattattttgwagagmctgggtct
6300  cacycykttgctwatgctggtctttgaacyccykgccycaarcartcctactccabcctc
6361  ccaargtgctggggatwataggcatgarctaaccgcacccagccccagacattttagtgt
6421  gtaaattcctgggcattttttcaaggcatcatacatgttagctgactgatgatggtcaat
6481  ttattttgtccatggtgtcaagtttctcttcaggaggaaaagcacagaactggccaagaa
6541  ttgcttgactgttctttaccatactgtttagCAGGAAACCAGTCTCAGTGTCCAACTCTC
6601  TAACCTTGGAACTGTGAGAACTCTGAGGACAAAGCAGCGGATACAACCTCAAAAGACGTC
6661  TGTCTACATTGAATTGGgtaagggtctcaggttttttaagtatttaataataattgctgg
6721  attccttatcttatagttttgccaaaaatcttggtcataatttgtatttgtggtaggcag
6781  ctttgggaagtgaattttatgagccctatggtgagttataaagaatgtaaaagacgcagt
6841  tcccaccttgaagaatcttactttaaaaagggagcaaaagaggccaggcatggtggctca
6901  cacctgtaatcccagcactttgggaggccaaagtgggtggatcacctgaggtcgggagtt
6961  cgagaccagcctagccaacatggagaaactctgtctgtaccaaaaaataaaaaattagcc
7021  aggtgtggtggcacataactgtaatcccagctactcgggaggctgaggcaggagaatcac
7081  ttgaacccgggaggtggaggttgcggtgaaccgagatcgcaccattgcactccagcctgg
7141  gcaaaaatagcgaactccatctaaaaaaaaaaaaagagagcaaaagaaagamtmtctggt
7201  tttaamtmtgtgtaaatatgtttttggaaagatggagagtagcaataagaaaaaacatga
7261    gattgctacagtatttagttccaagataaattgtactagatgaggaagccttttaaga
7321  agagctgaattgccaggcgcagtggctcacgcctgtaatcccagcactttgggaggccga
7381  ggtgggcggatcacctgaggtcgggagttcaagaccagcctgaccaacatggagaaaccc
7441  catctctactaaaaaaaaaaaaaaaaaaattagccggggtggtggcttatgcctgtaatc
7501  ccagctactcaggaggctgaggcaggagaatcgcttgaacccaggaagcagaggttgcag
7561  tgagccaagatcgcaccattgcactccagcctaggcaacaagagtgaaactccatctcaa
7621  aaaaaaaaaaaaagagctgaatcttggctgggcaggatggctcgtgcctgtaatcctaac
7681  gctttggaagaccgaggcagaaggattggttgagtccacgagtttaagaccagcctggcc
7741  aacataggggaaccctgtctctatttttaaaataataatacatttttggccggtgcggtg
7801  gctcatgcctgtaatcccaatactttgggaggctgaggcaggtagatcacctgaggtcag
7861  agttcgagaccagcctggataacctggtgaaacccctctttactaaaaatacaaaaaaaa
7921  aaaaaaattagctgggtgtggtagcacatgcttgtaatcccagctacttgggaggctgag
7981  gcaggagaatcgcttgaaccagggaggcggaggttacaatgagccaacactacaccactg
8041  cactccagcctgggcaatagagtgagactgcatctcaaaaaaataataatttttaaaaat
8101  aataaatttttttaagcttataaaaagaaaagttgaggccagcatagtagctcacatctg
8161  taatctcagcagtggcagaggattgcttgaagccaggagtttgagaccagcctgggcaac
8221  atagcaagacctcatctctacaaaaaaatttcttttttaaattagctgggtgtggtggtg
8281  tgcatctgtagtcccagctactcaggaggcagaggtgagtggatacattgaacccaggag
8341  tttgaggctgtagtgagctatgatcatgccactgcactccaacctgggtgacagagcaag
8401  acctccaaaaaaaaaaaaaaaagagctgctgagctcagaattcaaactgggctctcaaat
8461  tggattttcttttagaatatatttataattaaaaaggatagccatcttttgagctcccag
8521  gcaccaccatctatttatcataacacttactgttttccccccttatgatcataaattcct
8581  agacaacaggcattgtaaaaatagttatagtagttgatatttaggagcacttaactatat
8641  tccaggcactattgtgcttttcttgtataactcattagatgcttgtcagacctctgagat
8701  tgttcctattatacttattttacagatgagaaaattaaggcacagagaagttatgaaatt
8761  tttccaaggtattaaacctagtaagtggctgagccatgattcaaacctaggaagttagat
8821  gtcagagcctgtgcttttttttttgtttttgtttttgttttcagtagaaacggggtctca
8881  ctttgttggccaggctggtcttgaactcctaacctcaaataatccacccatctcggcctc
8941  ctcaagtgctgggattacaggtgagagccactgtgcctggcgaagcccatgcctttaacc
9001  acttctctgtattacatactagcttaactagcattgtacctgccacagtagatgctcagt
9061  aaatatttctagttgaatatctgtttttcaacaagtacatttttttaacccttttaatta
9121  agaaaacttttattgatttattttttggggggaaattttttagGATCTGATTCTTCTGAA
```

FIG. 10C

```
9181   GATACCGTTAATAAGGCAACTTATTGCAGgtgagtcaaagagaacctttgtctatgaagc
9241   tggtattttcctatttagttaatattaaggattgatgtttctctctttttaaaaatattt
9301   taacttttattttaggttcagggatgtatgtgcagtttgttatataggtaaacacacgac
9361   ttgggatttggtgtatagatttttttcatcatccgggtactaagcataccccacagtttt
9421   ttgtttgctttctttctgaatttctccctcttcccaccttcctccctcaagtaggctggt
9481   gtttctccagactagaatcatggtattggaagaaaccttagagatcatctagtttagttc
9541   tctcattttatagtggaggaaataccctttttgtttgttggatttagttattagcactgt
9601   ccaaaggaatttaggataacagtagaactctgcacatgcttgcttctagcagattgttct
9661   ctaagttcctcatatacagtaatattgacacagcagtaattgtgactgatgaaaatgttc
9721   aaggacttcattttcaactctttctttcctctgttccttatttccacatatctctcaagc
9781   tttgtctgtatgttatataataaactacaagcaaccccaactatgttacctaccttcctt
9841   aggaattattgcttgacccaggttttttttttttttttttggagacggggtcttgccct
9901   gttgccaggatggagtgtagtggcgccatctcggctcactgcaatctccaactccctggt
9961   tcaagcgattctcctgtctcaatctcacgagtagctgggactacaggtatacaccaccac
10021  gcccggttaattgaccattccatttctttctttctctcttttttttttttttttttgaga
10081  cagagtcttgctctgttgcccaggctggagtacagaggtgtgatctcacctctccgcaac
10141  gtctgcctcccaggttgaagccatactcctgcctcagcctctctagtagctgggactaca
10201  ggcgcgcgccaccacacccggctaatttttgtatttttagtagagatggggtttcaccat
10261  gttggccaggctggtcttgaactcatgacctcaagtggtccacccgcctcagcctcccaa
10321  agtgctggaattacaggcttgagccaccgtgcccagcaaccatttcatttcaactagaag
10381  tttctaaaggagagagcagctttcactaactaaataagattggtcagctttctgtaatcg
10441  aaagagctaaaatgtttgatcttggtcatttgacagttctgcatacatgtaactagtgtt
10501  tcttattaggactctgtcttttccctatagTGTGGGAGATCAAGAATTGTTACAAATCAC
10561  CCCTCAAGGAACCAGGGATGAAATCAGTTTGGATTCTGCAAAAAAGGgtaatggcaaagt
10621  ttgccaacttaacaggcactgaaaagagagtgggtagatacagtactgtaattagattat
10681  tctgaagaccatttgggacctttacaacccacaaaatctcttggcagagttagagtatca
10741  ttctctgtcaaatgtcgtggtatggtctgatagatttaaatggtactagactaatgtacc
10801  tataataagaccttcttgtaactgattgttgccctttcgcttttttttttgtttgtttgt
10861  ttgtttttttttgagatggggtctcactctgttgcccaggctggagtgcagtgatgcaat
10921  cttggctcactgcaacctccacctccaaaggctcaagctatcctcccacttcagcctcct
10981  gagtagctgggactacaggcgcatgccaccacacccggttaatttttgtggttttatag
11041  agatggggtttcaccatgttaccgaggctggtctcaaactcctggactcaagcagtctgc
11101  ccacttcagcctcccaaagtgctgcagttacaggcttgagccactgtgcctggcctgccc
11161  tttacttttaattggtgtatttgtgtttcatcttttacctactggtttttaaatataggg
11221  agtggtaagtctgtagatagaacagagtattaagtagacttaatggccagtaatctttag
11281  agtacatcagaaccagttttctgatggccaatctgcttttaattcactcttagacgttag
11341  agaaataggtgtggtttctgcatagggaaaattctgaaattaavvvvvvvvvvvvvgatc
11401  ctaagtggaaataatctaggtaaataggaattaaatgaaagagtatgagctacatcttca
11461  gtatacttggtagtttatgaggttagtttctctaatatagccagttggttgatttccacc
11521  tccaaggtgtatgaagtatgtatttttttaatgacaattcagtttttgagtaccttgtta
11581  tttttgtatattttcagCTGCTTGTGAATTTTCTGAGACGGATGTAACAAATACTGAACA
11641  TCATCAACCCAGTAATAATGATTTGAACACCACTGAGAAGCGTGCAGCTGAGAGGCATCC
11701  AGAAAAGTATCAGGGTAGTTCTGTTTCAAACTTGCATGTGGAGCCATGTGGCACAAATAC
11761  TCATGCCAGCTCATTACAGCATGAGAACAGCAGTTTATTACTCACTAAAGACAGAATGAA
11821  TGTAGAAAAGGCTGAATTCTGTAATAAAAGCAAACAGCCTGGCTTAGCAAGGAGCCAACA
11881  TAACAGATGGGCTGGAAGTAAGGAAACATGTAATGATAGGCGGACTCCCAGCACAGAAAA
11941  AAAGGTAGATCTGAATGCTGATCCCCTGTGTGAGAGAAAAGAATGGAATAAGCAGAAACT
12001  GCCATGCTCAGAGAATCCTAGAGATACTGAAGATGTTCCTTGGATAACACTAAATAGCAG
12061  CATTCAGAAAGTTAATGAGTGGTTTTCCAGAAGTGATGAACTGTTAGGTTCTGATGACTC
12121  ACATGATGGGGAGTCTGAATCAAATGCCAAAGTAGCTGATGTATTGGACGTTCTAAATGA
12181  GGTAGATGAATATTCTGGTTCTTCAGAGAAAATAGACTTACTGGCCAGTGATCCTCATGA
```

FIG. 10D

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12241  GGCTTTAATATGTAAAAGTGAAAGAGTTCACTCCAAATCAGTAGAGAGTAATATTGAAGG
12301  CCAAATATTTGGGAAAACCTATCGGAAGAAGGCAAGCCTCCCCAACTTAAGCCATGTAAC
12361  TGAAAATCTAATTATAGGAGCATTTGTTACTGAGCCACAGATAATACAAGAGCGTCCCCT
12421  CACAAATAAATTAAAGCGTAAAAGGAGACCTACATCAGGCCTTCATCCTGAGGATTTTAT
12481  CAAGAAAGCAGATTTGGCAGTTCAAAAGACTCCTGAAATGATAAATCAGGGAACTAACCA
12541  AACGGAGCAGAATGGTCAAGTGATGAATATTACTAATAGTGGTCATGAGAATAAAACAAA
12601  AGGTGATTCTATTCAGAATGAGAAAAATCCTAACCCAATAGAATCACTCGAAAAAGAATC
12661  TGCTTTCAAAACGAAAGCTGAACCTATAAGCAGCAGTATAAGCAATATGGAACTCGAATT
12721  AAATATCCACAATTCAAAAGCACCTAAAAAGAATAGGCTGAGGAGGAAGTCTTCTACCAG
12781  GCATATTCATGCGCTTGAACTAGTAGTCAGTAGAAATCTAAGCCCACCTAATTGTACTGA
12841  ATTGCAAATTGATAGTTGTTCTAGCAGTGAAGAGATAAAGAAAAAAAAGTACAACCAAAT
12901  GCCAGTCAGGCACAGCAGAAACCTACAACTCATGGAAGGTAAAGAACCTGCAACTGGAGC
12961  CAAGAAGAGTAACAAGCCAAATGAACAGACAAGTAAAAGACATGACAGCGATACTTTCCC
13021  AGAGCTGAAGTTAACAAATGCACCTGGTTCTTTTACTAAGTGTTCAAATACCAGTGAACT
13081  TAAAGAATTTGTCAATCCTAGCCTTCCAAGAGAAGAAAAAGAAGAGAAACTAGAAACAGT
13141  TAAAGTGTCTAATAATGCTGAAGACCCCAAAGATCTCATGTTAAGTGGAGAAAGGGTTTT
13201  GCAAACTGAAAGATCTGTAGAGAGTAGCAGTATTTCATTGGTACCTGGTACTGATTATGG
13261  CA[illegible]TCAGGAAAGTATCTCGTTACTGGAAGTTAGCACTCTAGGGAAGGCAAAAACAGAACC
13321  AAATAAATGTGTGAGTCAGTGTGCAGCATTTGAAAACCCCAAGGGACTAATTCATGGTTG
13381  TTCCAAAGATAATAGAAATGACACAGAAGGCTTTAAGTATCCATTGGGACATGAAGTTAA
13441  CCACAGTCGGGAAACAAGCATAGAAATGGAAGAAAGTGAACTTGATGCTCAGTATTTGCA
13501  GAATACATTCAAGGTTTCAAAGCGCCAGTCATTTGCTCCGTTTTCAAATCCAGGAAATGC
13561  AGAAGAGGAATGTGCAACATTCTCTGCCCACTCTGGGTCCTTAAAGAAACAAAGTCCAAA
13621  AGTCACTTTTGAATGTGAACAAAAGGAAGAAAATCAAGGAAAGAATGAGTCTAATATCAA
13681  GCCTGTACAGACAGTTAATATCACTGCAGGCTTTCCTGTGGTTGGTCAGAAAGATAAGCC
13741  AGTTGATAATGCCAAATGTAGTATCAAAGGAGGCTCTAGGTTTTGTCTATCATCTCAGTT
13801  CAGAGGCAACGAAACTGGACTCATTACTCCAAATAAACATGGACTTTTACAAAACCCATA
13861  TCGTATACCACCACTTTTTCCCATCAAGTCATTTGTTAAAACTAAATGTAAGAAAAATCT
13921  GCTAGAGGAAAACTTTGAGGAACATTCAATGTCACCTGAAAGAGAAATGGAAATGAGAA
13981  CATTCCAAGTACAGTGAGCACAATTAGCCGTAATAACATTAGAGAAAATGTTTTTAAAGA
14041  AGCCAGCTCAAGCAATATTAATGAAGTAGGTTCCAGTACTAATGAAGTGGGCTCCAGTAT
14101  TAATGAAATAGGTTCCAGTGATGAAAACATTCAAGCAGAACTAGGTAGAAACAGAGGGCC
14161  AAAATTGAATGCTATGCTTAGATTAGGGGTTTTGCAACCTGAGGTCTATAAACAAAGTCT
14221  TCCTGGAAGTAATTGTAAGCATCCTGAAATAAAAAAGCAAGAATATGAAGAAGTAGTTCA
14281  GACTGTTAATACAGATTTCTCTCCATATCTGATTTCAGATAACTTAGAACAGCCTATGGG
14341  AAGTAGTCATGCATCTCAGGTTTGTTCTGAGACACCTGATGACCTGTTAGATGATGGTGA
14401  AATAAAGGAAGATACTAGTTTTGCTGAAAATGACATTAAGGAAAGTTCTGCTGTTTTTAG
14461  CAAAAGCGTCCAGAAAGGAGAGCTTAGCAGGAGTCCTAGCCCTTTCACCCATACACATTT
14521  GGCTCAGGGTTACCGAAGAGGGGCCAAGAAATTAGAGTCCTCAGAAGAGAACTTATCTAG
14581  TGAGGATGAAGAGCTTCCCTGCTTCCAACACTTGTTATTTGGTAAAGTAAACAATATACC
14641  TTCTCAGTCTACTAGGCATAGCACCGTTGCTACCGAGTGTCTGTCTAAGAACACAGAGGA
14701  GAATTTATTATCATTGAAGAATAGCTTAAATGACTGCAGTAACCAGGTAATATTGGCAAA
14761  GGCATCTCAGGAACATCACCTTAGTGAGGAAACAAAATGTTCTGCTAGCTTGTTTTCTTC
14821  ACAGTGCAGTGAATTGGAAGACTTGACTGCAAATACAAACACCCAGGATCCTTTCTTGAT
14881  TGGTTCTTCCAAACAAATGAGGCATCAGTCTGAAAGCCAGGGAGTTGGTCTGAGTGACAA
14941  GGAATTGGTTTCAGATGATGAAGAAAGAGGAACGGGCTTGGAAGAAAATAATCAAGAAGA
15001  GCAAAGCATGGATTCAAACTTAGgtattggaaccaggttttgtgtttgccccagtctat
15061  ttatagaagtgagctaaatgtttatgcttttggggagcacattttacaaatttccaagta
15121  tagttaaaggaactgcttcttaaacttgaaacatgttcctcctaaggtgcttttcataga
15181  aaaaagtccttcacacagctaggacgtcatctttgactgaatgagctttaacatcctaat
15241  tactggtggacttacttctggtttcattttataaagcaaatcccggtgtcccaaagcaag
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FIG. 10E

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15301  gaatttaatcattttgtgtgacatgaaagtaaatccagtcctgccaatgagaagaaaaag
15361  acacagcaagttgcagcgtttatagtctgcttttacatctgaacctctgtttttgttatt
15421  taagGTGAAGCAGCATCTGGGTGTGAGAGTGAAACAAGCGTCTCTGAAGACTGCTCAGGG
15481  CTATCCTCTCAGAGTGACATTTTAACCACTCaggtaaaaagcgtgtgtgtgtgtgcacat
15541  gcgtgtgtgtggtgtcctttgcattcagtagtatgtatcccacattcttaggtttgctga
15601  catcatctctttgaattaatggcacaattgtttgtggttcattgtcvvvvvvvvvvvvvn
15661  gngaatgtaatcctaatatttcncnccnacttaaaagaataccactccaanggcatcnca
15721  atacatcaatcaattggggaattgggattttccctcnctaacatcantggaataatttca
15781  tggcattaattgcatgaatgtggttagattaaaggtgttcatgctagaacttgtagttc
15841  catactaggtgatttcaattcctgtgctaaaattaatttgtatgatatattntcatttaa
15901  tggaaagcttctcaaagtatttcatttcttggtaccatttatcgtttttgaAGCAGAGG
15961  GATACCATGCAACATAACCTGATAAAGCTCCAGCAGGAAATGGCTGAACTAGAAGCTGTG
16021  TTAGAACAGCATGGGAGCCAGCCTTCTAACAGCTACCCTTCCATCATAAGTGACTCTTCT
16081  GCCCTTGAGGACCTGCGAAATCCAGAACAAAGCACATCAGAAAAAGgtgtgtattgttgg
16141  ccaaacactgatatcttaagcaaaattctttccttcccctttatctccttctgaagagta
16201  aggacctagctccaacattttatgatccttgctcagcacatgggtaattatggagccttg
16261  gttcttgtccctgctcacaactaatataccagtcagagggacccaaggcagtcattcatg
16321  ttgtcatctgagatacctacaacaagtagatgctatggggagcccatggvvvvvvvvvvv
16381  vvccattggtgctagcatctgtctgttgcattgcttgtgtttataaattctgcctgata
16441  tacttgttaaaaaccaatttgtgtatcatagattgatgcttttgaaaaaaatcagtattc
16501  taacctgaattatcactatcagaacaaagcagtaaagtagatttgttttctcattccatt
16561  taaagCAGTATTAACTTCACAGAAAAGTAGTGAATACCCTATAAGCCAGAATCCAGAAGG
16621  CCTTTCTGCTGACAAGTTTGAGGTGTCTGCAGATAGTTCTACCAGTAAAAATAAAGAACC
16681  AGGAGTGGAAAGgtaagaaacatcaatgtaaagatgctgtggtatctgacatctttattt
16741  atattgaactctgattgttaatttttttcaccatactttctccagtttttttgcatacag
16801  gcatttatacacttttattgctctaggatacttcttttgtttaatcctatataggvvvvv
16861  vvvvvvvvvggataagntcaagagatatttgataggtgatgcagtgatnaattgngaaaa
16921  tttnctgcctgcttttaatcttccccgttctttcttcctncctccctcccttcctncct
16981  cccgtccttncctttcctttccctcccttccnccttctttccntctntctttccttttctt
17041  tcctgtctacctttctttccttcctcccttcctttttctttttctttctttcctttcctttt
17101  ctttcctttctttcctttcctttctttcttgacagagtcttgctctgtcactcaggctgg
17161  agtgcagtggcgtgatctcgnctcactgcaacctctgtctcccaggttcaagcaatttc
17221  ctgcctcagcctcccgagtagctgagattacaggcgccagccaccacacccagctactga
17281  cctgcttttvvvvvvvvvvvvvvaaacagctgggagatatggtgcctcagaccaagccat
17341  gttatatgtcaaccctgacatattggcaggcaacatgaatccagacttctaggctgtcat
17401  gcgggctctttttttgccagtcatttctgatctctctgacatgagctgtttcatttatgct
17461  ttggctgcccaggaagtatgatttgtcctttcacaattggtggcgatggttttctccttc
17521  catttatctttctagGTCATCCCCTTCTAAATGCCCATCATTAGATGATAGGTGGTACAT
17581  GCACAGTTGCTCTGGGAGTCTTCAGAATAGAAACTACCCATCTCAAGAGGAGCTCATTAA
17641  GGTTGTTGATGTGGAGGAGCAACAGCTGGAAGAGTCTGGGCCACACGATTTGACGGAAAC
17701  ATCTTACTTGCCAAGGCAAGATCTAGgtaatatttcatctgctgtattggaacaaacact
17761  ytgattttactctgaatcctacataaagatattctggttaaccaacttttagatgtacta
17821  gtctatcatggacacttttgttatacttaattaagcccactttagaaaaatagctcaagt
17881  gttaatcaaggtttacttgaaaattattgaaactgttaatccatctatattttaattaat
17941  ggtttaactaatgattttgaggatgwgggagtcktggtgtactctamatgtattatttca
18001  ggccaggcatagtggctcacgcctggtaatcccagtayycmrgagcccgaggcaggtgga
18061  gccagctgaggtcaggagttcaagacctgtcttggccaacatgggngaaaccctgtcttc
18121  ttcttaaaaaanacaaaaaaaattaactgggttgtgcttaggtgnatgccccgnatccta
18181  gttnttcttgngggttgagggaggagatcacnttggaccccggaggggngggtgggggng
18241  agcaggncaaaacacngacccagctggggtggaagggaagcccactcnaaaaaannttnv
18301  vvvvvvvvvvvvvttttaggaaacaagctactttggatttccaccaacacctgtattcat
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FIG. 10F

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18361 gtacccccattttctcttaacctaactttattggtctttttaattcttaacagagaccaga
18421 actttgtaattcaacattcatcgttgtgtaaattaaacttctcccattcctttcagAGGG
18481 AACCCCTTACCTGGAATCTGGAATCAGCCTCTTCTCTGATGACCCTGAATCTGATCCTTC
18541 TGAAGACAGAGCCCCAGAGTCAGCTCGTGTTGGCAACATACCATCTTCAACCTCTGCATT
18601 GAAAGTTCCCCAATTGAAAGTTGCAGAATCTGCCCAGAGTCCAGCTGCTGCTCATACTAC
18661 TGATACTGCTGGGTATAATGCAATGGAAGAAAGTGTGAGCAGGGAGAAGCCAGAATTGAC
18721 AGCTTCAACAGAAAGGGTCAACAAAAGAATGTCCATGGTGGTGTCTGGCCTGACCCCAGA
18781 AGAATTTgtgagtgtatccatatgtatctccctaatgactaagacttaacaacattctgg
18841 aaagagttttatgtaggtattgtcaattaataacctagaggaagaaatctagaaaacaat
18901 cacagttctgtgtaatttaatttcgattactaatttctgaaaatttagaayvvvvvvvvv
18961 vvvvncccnnccccccnaatctgaaatgggggtaacccccccccaaccganacntgggtng
19021 cntagagantttaatggcccnttctgaggnacanaagcttaagccaggngacgtggancn
19081 atgngttgtttnttgtttggttacctccagcctgggtgacagagcaagactctgtctaaa
19141 aaaaaaaaaaaaaaaatcgactttaaatagttccaggacacgtgtagaacgtgcaggat
19201 tgctacgtaggtaaacatatgccatggtgggataactagtattctgagctgtgtgctaga
19261 ggtaactcatgataatggaatatttgatttaatttcagATGCTCGTGTACAAGTTTGCCA
19321 GAAAACACCACATCACTTTAACTAATCTAATTACTGAAGAGACTACTCATGTTGTTATGA
19381 AAACAGgtataccaagaacctttacagaataccttgcatctgctgcataaaaccacatga
19441 ggcgaggcacggtggcgcatgcctgtaatcgcagcactttgggaggccgaggcgggcaga
19501 tcacgagattaggagatcgagaccatcctggccagcatggtgaaaccccgtctctactan
19561 naaatggnaaaattanctgggtgtggtcgcgtgcncctgtagtcccagctactcgtgagg
19621 ctgaggcaggagaatcacttgaaccggggaaatggaggtttcagtgagcagagatcatnc
19681 ccctncattccagcctggcgacagagcaaggctccgtcnccnaaaaaataaaaaaaaacg
19741 tgaacaaataagaatatttgttgagcatagcatggatgatagtcttctaatagtcaatca
19801 attactttatgaaagacaaataatagttttgctgcttccttacctccttttgttttgggt
19861 taagatttggagtgtgggccaggcacvvvvvvvvvvvvvvgatctatagctagccttggcg
19921 tctagaagatgggtgttgagaagagggagtggaaagatatttcctctggtcttaacttca
19981 tatcagcctcccctagacttccaaatatccatacctgctggttataattagtggtgtttt
20041 cagcctctgattctgtcaccaggggttttagaatcataaatccagattgatcttgggagt
20101 gtaaaaaactgaggctctttagcttcttaggacagcagttcctgattttgttttcaactt
20161 ctaatcctttgagtgtttttcattctgcagATGCTGAGTTTGTGTGTGAACGGACACTGA
20221 AATATTTTCTAGGAATTGCGGGAGGAAAATGGGTAGTTAGCTATTTCTgtaagtataata
20281 ctatttctcccctcctccctttaacacctcagaattgcattttttacacctaacatttaac
20341 acctaaggttttgctgatgctgagtctgagttaccaaaaggtctttaaattgtaatact
20401 aaactacttttatctttaatatcactttgttcaagataagctggtgatgctgggaaaatg
20461 ggtctcttttataactaataggacctaatctgctcctagcaatgttagcatatgagctag
20521 ggatttatttaatagtcggcaggaatccatgtgcarcagncaaacttataatgtttaaat
20581 taaacatcaactctgtctccagaaggaaactgctgctacaagccttattaaagggctgtg
20641 gctttagagggaaggacctctcctctgtcattcttcctgtgctcttttgtgaatcgctga
20701 cctctctatctccgtgaaaagagcacgttcttctgctgtatgtaacctgtcttttctatg
20761 atctctvvvvvvvvvvvvvvnaaaaacggggnngggantgggccttaaanccaaagggcna
20821 actccccaaccattnaaaaantgacnggggattattaaaancggcgggaaacatttcacn
20881 gcccaactaatattgttaaattaaaaccaccaccnctgcnccaaggagggaaactgctgc
20941 tacaagccttattaaagggctgtggctttagagggaaggacctctcctctgtcattcttc
21001 ctgtgctcttttgtgaatcgctgacctctctatgtccgtgaaaagagcacgttcttcgtc
21061 tgtatgtaacctgtcttttctatgatctctttagGGGTGACCCAGTCTATTAAAGAAAGA
21121 AAAATGCTGAATGAGgtaagtacttgatgttacaaactaaccagagatattcattcagtc
21181 atatagttaaaaatgtatttgcttccttccatcaatgcaccactttccttaacaatgcac
21241 aaattttccatgataatgaggatcatcaagaattatgcaggcctgcactgtggctcatac
21301 ctataatcccagcgctttgggaggctgaggcgcttggatcvvvvvvvvvvvvvvaatttt
21361 tgtatttttagtagagatgaggttcaccatgttggtctagatctggtgtcgaacgtcctg
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FIG. 10G

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21421  acctcaagtgatctgccagcctcagtctcccaaagtgctaggattacaggggtgagccac
21481  tgcgcctggcctgaatgcctaaaatatgacgtgtctgctccacttccattgaaggaagct
21541  tctctttctcttatcctgatgggttgtgtttggtttctttcagCATGATTTTGAAGTCAG
21601  AGGAGATGTGGTCAATGGAAGAAACCACCAAGGTCCAAAGCGAGCAAGAGAATCCCAGGA
21661  CAGAAAGgtaaagctccctccctcaagttgacaaaaatctcaccccaccactctgtattc
21721  cactcccctttgcagagatgggccgcttcatttgtaagacttattacatacatacacag
21781  tgctagatactttcacacaggttctttttcactcttccatcccaaccacataaataagt
21841  attgtctctactttatgaatgataaaactaagagatttagagaggctgtgtaatttggat
21901  tcccgtctcgggttcagatcvvvvvvvvvvvvvttggcctgattggtgacaaaagtgaga
21961  tgctcagtccttgaatgacaaagaatgcctgtagagttgcaggtccaactacatatgcac
22021  ttcaagaagatcttctgaaatctagtagtgttctggacattggactgcttgtccctggga
22081  agtagcagcagaaatgatcggtggtgaacagaagaaaaagaaaagctcttcctttttgaa
22141  agtctgtttttgaataaaagccaatattcttttataactagatttccttctctccatt
22201  cccctgtccctctctcttcctctcttcttccagATCTTCAGGGGGCTAGAAATCTGTTGC
22261  TATGGGCCCTTCACCAACATGCCCACAGgtaagagcctgggagaaccccagagttccagc
22321  accagcctttgtcttacatagtggagtattataagcaaggtcccacgatgggggttcctc
22381  agattgctgaaatgttctagaggctattctatttctctaccactctccaaacaaaacagc
22441  acctaaatgttatcctatggcaaaaaaaaactataccttgtcccccttctcaagagcatg
22501  aaggtggttaatagttaggattcagtatgttatgtgttcagatggcgttgagctgctgtt
22561  agtgccvvvvvvvvvvvvvtttgagagactatcaaaccttataccaagtggccttatgga
22621  gactgataaccagagtacatggcatatcagtggcaaattgacttaaaatccataccccta
22681  ctattttaagaccattgtcctttggagcagagagacagactctcccattgagaggtcttg
22741  ctataagccttcatccggagagtgtagggtagagggcctgggttaagtatgcagattact
22801  gcagtgattttacatgtaaatgtccatttagATCAACTGGAATGGATGGTACAGCTGTG
22861  TGGTGCTTCTGTGGTGAAGGAGCTTTCATCATTCACCCTTGGCACAgtaagtattgggtg
22921  ccctgtcagtgtgggaggacacaatattctctcctgtgagcaagactggcacctgtcagt
22981  ccctatggatgcccctactgtagcctcagaagtcttctctgcccacatacctgtgccaaa
23041  agactccatvvvvvvvvvvvvvggtggtacgtgtctgtagttccagctacttgggaggct
23101  gagatggaaggattgcttgagcccaggaggcagaggtggnannttacgctgagatcacac
23161  cactgcactccagcctgggtgacagagcaagaccctgtctcaaaaacaaacaaaaaaaat
23221  gatgaagtgacagttccagtagtcctactttgacactttgaatgctctttccttcctggg
23281  gatccagGGTGTCCACCCAATTGTGGTTGTGCAGCCAGATGCCTGGACAGAGGACAATGG
23341  CTTCCATGgtaaggtgcctcgcatgtacctgtgctattagtggggtccttgtgcatgggt
23401  ttggtttatcactcattacctggtgcttgagtagcacagttcttggcacattttaaata
23461  tttgttgaatgaatggctaaaatgtctttttgatgttttattgttatttgttttatatt
23521  gtaaaagtaatacatgaactgtttccatggggtgggagtaagatatgaatgttcatcacv
23581  vvvvvvvvvvvvcagtaatcctnagaactcatacgaccgggcccctggagtcgntgnttn
23641  gagcctagtccnggagaatgaattgacactaatctctgcttgtgttctctgtctccagCA
23701  ATTGGGCAGATGTGTGAGGCACCTGTGGTGACCCGAGAGTGGGTGTTGGACAGTGTAGCA
23761  CTCTACCAGTGCCAGGAGCTGGACACCTACCTGATACCCCAGATCCCCCACAGCCACTAC
23821  TGACTGCAGCCAGCCACAGGTACAGAGCCACAGGACCCCAAGAATGAGCTTACAAAGTGG
23881  CCTTTCCAGGCCCTGGGAGCTCCTCTCACTCTTCAGTCCTTCTACTGTCCTGGCTACTAA
23941  ATATTTTATGTACATCAGCCTGAAAAGGACTTCTGGCTATGCAAGGGTCCCTTAAAGATT
24001  TTCTGCTTGAAGTCTCCCTTGGAAAT
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FIG. 10H

17Q-LINKED BREAST AND OVARIAN CANCER SUSCEPTIBILITY GENE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of application Ser. No. 08/409,305 filed on 24 Mar. 1995, abandoned, which is a continuation-in-part of application Ser. No. 08/348,824 filed on 29 Nov. 1994, abandoned, which is a continuation-in-part of application Ser. No. 08/308,104 filed on 16 Sep. 1994, which is a continuation-in-part of application Ser. No. 08/300,266, filed on 2 Sep. 1994, abandoned, which is a continuation-in-part of application Ser. No. 08/289,221, filed on 12 Aug. 1994, abandoned, all incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates generally to the field of human genetics. Specifically, the present invention relates to methods and materials used to isolate and detect a human breast and ovarian cancer predisposing gene (BRCA1), some mutant alleles of which cause susceptibility to cancer, in particular, breast and ovarian cancer. More specifically, the invention relates to germline mutations in the BRCA1 gene and their use in the diagnosis of predisposition to breast and ovarian cancer. The present invention further relates to somatic mutations in the BRCA1 gene in human breast and ovarian cancer and their use in the diagnosis and prognosis of human breast and ovarian cancer. Additionally, the invention relates to somatic mutations in the BRCA1 gene in other human cancers and their use in the diagnosis and prognosis of human cancers. The invention also relates to the therapy of human cancers which have a mutation in the BRCA1 gene, including gene therapy, protein replacement therapy and protein mimetics. The invention further relates to the screening of drugs for cancer therapy. Finally, the invention relates to the screening of the BRCA1 gene for mutations, which are useful for diagnosing the predisposition to breast and ovarian cancer.

The publications and other materials used herein to illuminate the background of the invention, and in particular, cases to provide additional details respecting the practice, are incorporated herein by reference, and for convenience, are referenced by author and date in the following text and respectively grouped in the appended List of References.

BACKGROUND OF THE INVENTION

The genetics of cancer is complicated, involving multiple dominant, positive regulators of the transformed state (oncogenes) as well as multiple recessive, negative regulators (tumor suppressor genes). Over one hundred oncogenes have been characterized. Fewer than a dozen tumor suppressor genes have been identified, but the number is expected to increase beyond fifty (Knudson, 1993).

The involvement of so many genes underscores the complexity of the growth control mechanisms that operate in cells to maintain the integrity of normal tissue. This complexity is manifest in another way. So far, no single gene has been shown to participate in the development of all, or even the majority of human cancers. The most common oncogenic mutations are in the H-ras gene, found in 10–15% of all solid tumors (Anderson et al., 1992). The most frequently mutated tumor suppressor genes are the TP53 gene, homozygously deleted in roughly 50% of all tumors, and CDKN2, which was homozygously deleted in 46% of tumor cell lines examined (Kamb et al., 1994). Without a target that is common to all transformed cells, the dream of a "magic bullet" that can destroy or revert cancer cells while leaving normal tissue unharmed is improbable. The hope for a new generation of specifically targeted antitumor drugs may rest on the ability to identify tumor suppressor genes or oncogenes that play general roles in control of cell division.

The tumor suppressor genes which have been cloned and characterized influence susceptibility to: 1) Retinoblastoma (RB1); 2) Wilms' tumor (WT1); 3) Li-Fraumeni (TP53); 4) Familial adenomatus polyposis (APC); 5) Neurofibromatosis type 1 (NF1); 6) Neurofibromatosis type 2 (NF2); 7 von Hippel-Lindau syndrome (VHL); 8) Multiple endocrine neoplasia type 2A (MEN2A); and 9) Melanoma (CDKN2).

Tumor suppressor loci that have been mapped genetically but not yet isolated include genes for: Multiple endocrine neoplasia type 1 (MEN1); Lynch cancer family syndrome 2 (LCFS2); Neuroblastoma (NB); Basal cell nevus syndrome (BCNS); Beckwith-Wiedemann syndrome (BWS); Renal cell carcinoma (RCC); Tuberous sclerosis 1 (TSC1); and Tuberous sclerosis 2 (TSC2). The tumor suppressor genes that have been characterized to date encode products with similarities to a variety of protein types, including DNA binding proteins (WT1), ancillary transcription regulators (RB1), GTPase activating proteins or GAPs (NF1), cytoskeletal components (NF2), membrane bound receptor kinases (MEN2A), cell cycle regulators (CDKN2) and others with no obvious similarity to known proteins (APC and VHL).

In many cases, the tumor suppressor gene originally identified through genetic studies has been shown to be lost or mutated in some sporadic tumors. This result suggests that regions of chromosomal aberration may signify the position of important tumor suppressor genes involved both in genetic predisposition to cancer and in sporadic cancer.

One of the hallmarks of several tumor suppressor genes characterized to date is that they are deleted at high frequency in certain tumor types. The deletions often involve loss of a single allele, a so-called loss of heterozygosity (LOH), but may also involve homozygous deletion of both alleles. For LOH, the remaining allele is presumed to be nonfunctional, either because of a preexisting inherited mutation, or because of a secondary sporadic mutation.

Breast cancer is one of the most significant diseases that affects women. At the current rate, American women have a 1 in 8 risk of developing breast cancer by age 95 (American Cancer Society, 1992). Treatment of breast cancer at later stages is often futile and disfiguring, making early detection a high priority in medical management of the disease. Ovarian cancer, although less frequent than breast cancer is often rapidly fatal and is the fourth most common cause of cancer mortality in American women. Genetic factors contribute to an ill-defined proportion of breast cancer incidence, estimated to be about 5% of all cases but approximately 25% of cases diagnosed before age 40 (Claus et al., 1991). Breast cancer has been subdivided into two types, early-age onset and late-age onset, based on an inflection in the age-specific incidence curve around age 50. Mutation of one gene, BRCA1, is thought to account for approximately 45% of familial breast cancer, but at least 80% of families with both breast and ovarian cancer (Easton et al., 1993).

Intense efforts to isolate the BRCA1 gene have proceeded since it was first mapped in 1990 (Hall et al., 1990; Narod et al., 1991). A second locus, BRCA2, has recently been mapped to chromosome 13q (Wooster et al., 1994) and appears to account for a proportion of early-onset breast cancer roughly equal to BRCA1, but confers a lower risk of ovarian cancer. The remaining susceptibility to early-onset breast cancer is divided between as yet unmapped genes for familial cancer, and rarer germline mutations in genes such as TP53 (Malkin et al., 1990). It has also been suggested that heterozygote carriers for defective forms of the Ataxia-Telangectasia gene are at higher risk for breast cancer (Swift et al., 1976; Swift et al., 1991). Late-age onset breast cancer is also often familial although the risks in relatives are not as high as those for early-onset breast cancer (Cannon-Albright et al., 1994; Mettlin et al., 1990). However, the percentage of such cases due to genetic susceptibility is unknown.

Breast cancer has long been recognized to be, in part, a familial disease (Anderson, 1972). Numerous investigators have examined the evidence for genetic inheritance and concluded that the data are most consistent with dominant inheritance for a major susceptibility locus or loci (Bishop and Gardner, 1980; Go et al., 1983; Williams and Anderson, 1984; Bishop et al., 1988; Newman et al., 1988; Claus et al., 1991). Recent results demonstrate that at least three loci exist which convey susceptibility to breast cancer as well as other cancers. These loci are the TP53 locus on chromosome 17p (Malkin et al., 1990), a 17q-linked susceptibility locus known as BRCA1 (Hall et al., 1990), and one or more loci responsible for the unmapped residual. Hall et al. (1990) indicated that the inherited breast cancer susceptibility in kindreds with early age onset is linked to chromosome 17q21; although subsequent studies by this group using a more appropriate genetic model partially refuted the limitation to early onset breast cancer (Margaritte et al., 1992).

Most strategies for cloning the 17q-linked breast cancer predisposing gene (BRCA1) require precise genetic localization studies. The simplest model for the functional role of BRCA1 holds that alleles of BRCA1 that predispose to cancer are recessive to wild type alleles; that is, cells that contain at least one wild type BRCA1 allele are not cancerous. However, cells that contain one wild type BRCA1 allele and one predisposing allele may occasionally suffer loss of the wild type allele either by random mutation or by chromosome loss during cell division (nondisjunction). All the progeny of such a mutant cell lack the wild type function of BRCA1 and may develop into tumors. According to this model, predisposing alleles of BRCA1 are recessive, yet susceptibility to cancer is inherited in a dominant fashion: women who possess one predisposing allele (and one wild type allele) risk developing cancer, because their mammary epithelial cells may spontaneously lose the wild type BRCA1 allele. This model applies to a group of cancer susceptibility loci known as tumor suppressors or antioncogenes, a class of genes that includes the retinoblastoma gene and neurofibromatosis gene. By inference this model may also explain the BRCA1 function, as has recently been suggested (Smith et al., 1992).

A second possibility is that BRCA1 predisposing alleles are truly dominant; that is, a wild type allele of BRCA1 cannot overcome the tumor forming role of the predisposing allele. Thus, a cell that carries both wild type and mutant alleles would not necessarily lose the wild type copy of BRCA1 before giving rise to malignant cells. Instead, mammary cells in predisposed individuals would undergo some other stochastic change(s) leading to cancer.

If BRCA1 predisposing alleles are recessive, the BRCA1 gene is expected to be expressed in normal mammary tissue but not functionally expressed in mammary tumors. In contrast, if BRCA1 predisposing alleles are dominant, the wild type BRCA1 gene may or may not be expressed in normal mammary tissue. However, the predisposing allele will likely be expressed in breast tumor cells.

The 17q linkage of BRCA1 was independently confirmed in three of five kindreds with both breast cancer and ovarian cancer (Narod et al., 1991). These studies claimed to localize the gene within a very large region, 15 centiMorgans (cM), or approximately 15 million base pairs, to either side of the linked marker pCMM86 (D17S74). However, attempts to define the region further by genetic studies, using markers surrounding pCMM86, proved unsuccessful. Subsequent studies indicated that the gene was considerably more proximal (Easton et al., 1993) and that the original analysis was flawed (Margaritte et al., 1992). Hall et al., (1992) recently localized the BRCA1 gene to an approximately 8 cM interval (approximately 8 million base pairs) bounded by Mfd15 (D17S250) on the proximal side and the human GIP gene on the distal side. A slightly narrower interval for the BRCA1 locus, based on publicly available data, was agreed upon at the Chromosome 17 workshop in March of 1992 (Fain, 1992). The size of these regions and the uncertainty associated with them has made it exceedingly difficult to design and implement physical mapping and/or cloning strategies for isolating the BRCA1 gene.

Identification of a breast cancer susceptibility locus would permit the early detection of susceptible individuals and greatly increase our ability to understand the initial steps which lead to cancer. As susceptibility loci are often altered during tumor progression, cloning these genes could also be important in the development of better diagnostic and prognostic products, as well as better cancer therapies.

SUMMARY OF THE INVENTION

The present invention relates generally to the field of human genetics. Specifically, the present invention relates to methods and materials used to isolate and detect a human breast cancer predisposing gene (BRCA1), some alleles of which cause susceptibility to cancer, in particular breast and ovarian cancer. More specifically, the present invention relates to germline mutations in the BRCA1 gene and their use in the diagnosis of predisposition to breast and ovarian cancer. The invention further relates to somatic mutations in the BRCA1 gene in human breast cancer and their use in the diagnosis and prognosis of human breast and ovarian cancer. Additionally, the invention relates to somatic mutations in the BRCA1 gene in other human cancers and their use in the diagnosis and prognosis of human cancers. The invention also relates to the therapy of human cancers which have a mutation in the BRCA1 gene, including gene therapy, protein replacement therapy and protein mimetics. The invention further relates to the screening of drugs for cancer therapy. Finally, the invention relates to the screening of the BRCA1 gene for mutations, which are useful for diagnosing the predisposition to breast and ovarian cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a diagram showing the order of loci neighboring BRCA1 as determined by the chromosome 17 workshop. FIG. 1 is reproduced from Fain, 1992.

FIG. 2 is a schematic map of YACs which define part of Mfd15-Mfd188 region.

FIG. 3 is a schematic map of STSs, P1s and BACs in the BRCA1 region.

FIG. 4 is a schematic map of human chromosome 17. The pertinent region containing BRCA1 is expanded to indicate the relative positions of two previously identified genes, CA125 and RNU2. BRCA1 spans the marker D17S855.

FIG. 5 shows alignment of the BRCA1 zinc-finger domain with 3 other zinc-finger domains that scored highest in a Smith-Waterman alignment. RPT1 encodes a protein that appears to be a negative regulator of the IL-2 receptor in mouse. RIN1 encodes a DNA-binding protein that includes a RING-finger motif related to the zinc-finger. RFP1 encodes a putative transcription factor that is the N-terminal domain of the RET oncogene product. The bottom line contains the C3HC4 consensus zinc-finger sequence showing the positions of cysteines and one histidine that form the zinc ion binding pocket.

FIG. 6 is a diagram of BRCA1 mRNA showing the locations of introns and the variants of BRCA1 mRNA produced by alternative splicing. Intron locations are shown by dark triangles and the exons are numbered below the line representing the cDNA. The top cDNA is the composite used to generate the peptide sequence of BRCA1. Alternative forms identified as cDNA clones or hybrid selection clones are shown below.

FIG. 7 shows the tissue expression pattern of BRCA1. The blot was obtained from Clontech and contains RNA from the indicated tissues. Hybridization conditions were as recommended by the manufacturer using a probe consisting of nucleotide positions 3631 to 3930 of BRCA1. Note that both breast and ovary are heterogeneous tissues and the percentage of relevant epithelial cells can be variable. Molecular weight standards are in kilobases.

FIG. 8 is a diagram of the 5' untranslated region plus the beginning of the translated region of BRCA1 showing the locations of introns and the variants of BRCA1 mRNA produced by alternative splicing. Intron locations are shown by broken dashed lines. Six alternate splice forms are shown.

FIG. 9A shows a nonsense mutation in Kindred 2082. P indicates the person originally screened, b and c are haplotype carriers, a, d, e, f, and g do not carry the BRCA1 haplotype. The C to T mutation results in a stop codon and creates a site for the restriction enzyme AvrII. PCR amplification products are cut with this enzyme. The carriers are heterozygous for the site and therefore show three bands. Non-carriers remain uncut.

FIG. 9B shows a mutation and cosegregation analysis in BRCA1 kindreds. Carrier individuals are represented as filled circles and squares in the pedigree diagrams. Frameshift mutation in Kindred 1910. The first three lanes are control, noncarrier samples. Lanes labeled 1-3 contain sequences from carrier individuals. Lane 4 contains DNA from a kindred member who does not carry the BRCA1 mutation. The diamond is used to prevent identification of the kindred. The frameshift resulting from the additional C is apparent in lanes labeled 1, 2, and 3.

FIG. 9C shows a mutation and cosegregation analysis in BRCA1 kindreds. Carrier individuals are represented as filled circles and squares in the pedigree diagrams. Inferred regulatory mutation in Kindred 2035. ASO analysis of carriers and noncarriers of 2 different polymorphisms (PM1 and PM7) which were examined for heterozygosity in the germline and compared to the heterozygosity of lymphocyte mRNA. The top 2 rows of each panel contain PCR products amplified from genomic DNA and the bottom 2 rows contain PCR products amplified from cDNA. "A" and "G" are the two alleles detected by the ASO. The dark spots indicate that a particular allele is present in the sample. The first three lanes of PM7 represent the three genotypes in the general population.

FIG. 10A-10H show genomic sequence of BRCA1. The lower case letters denote intron sequence while the upper case letters denote exon sequence. Indefinite intervals within introns are designated with vvvvvvvvvvvvv. Known polymorphic sites are shown as underlined and boldface type.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates generally to the field of human genetics. Specifically, the present invention relates to methods and materials used to isolate and detect a human breast cancer predisposing gene (BRCA1), some alleles of which cause susceptibility to cancer, in particular breast and ovarian cancer. More specifically, the present invention relates to germline mutations in the BRCA1 gene and their use in the diagnosis of predisposition to breast and ovarian cancer. The invention further relates to somatic mutations in the BRCA 1 gene in human breast cancer and their use in the diagnosis and prognosis of human breast and ovarian cancer. Additionally, the invention relates to somatic mutations in the BRCA1 gene in other human cancers and their use in the diagnosis and prognosis of human cancers. The invention also relates to the therapy of human cancers which have a mutation in the BRCA1 gene, including gene therapy, protein replacement therapy and protein mimetics. The invention further relates to the screening of drugs for cancer therapy. Finally, the invention relates to the screening of the BRCA1 gene for mutations, which are useful for diagnosing the predisposition to breast and ovarian cancer.

The present invention provides an isolated polynucleotide comprising all, or a portion of the BRCA1 locus or of a mutated BRCA1 locus, preferably at least eight bases and not more than about 100 kb in length. Such polynucleotides may be antisense polynucleotides. The present invention also provides a recombinant construct comprising such an isolated polynucleotide, for example, a recombinant construct suitable for expression in a transformed host cell.

Also provided by the present invention are methods of detecting a polynucleotide comprising a portion of the BRCA1 locus or its expression product in an analyte. Such methods may further comprise the step of amplifying the portion of the BRCA1 locus, and may further include a step of providing a set of polynucleotides which are primers for amplification of said portion of the BRCA1 locus. The method is useful for either diagnosis of the predisposition to cancer or the diagnosis or prognosis of cancer.

The present invention also provides isolated antibodies, preferably monoclonal antibodies, which specifically bind to an isolated polypeptide comprised of at least five amino acid residues encoded by the BRCA1 locus.

The present invention also provides kits for detecting in an analyte a polynucleotide comprising a portion of the BRCA1 locus, the kits comprising a polynucleotide complementary to the portion of the BRCA1 locus packaged in a suitable container, and instructions for its use.

The present invention further provides methods of preparing a polynucleotide comprising polymerizing nucleotides to yield a sequence comprised of at least eight consecutive nucleotides of the BRCA1 locus; and methods of preparing a polypeptide comprising polymerizing amino acids to yield a sequence comprising at least five amino acids encoded within the BRCA1 locus.

The present invention further provides methods of screening the BRCA1 gene to identify mutations. Such methods may further comprise the step of amplifying a portion of the BRCA1 locus, and may further include a step of providing a set of polynucleotides which are primers for amplification of said portion of the BRCA1 locus. The method is useful for identifying mutations for use in either diagnosis of the predisposition to cancer or the diagnosis or prognosis of cancer.

The present invention further provides methods of screening suspected BRCA1 mutant alleles to identify mutations in the BRCA1 gene.

In addition, the present invention provides methods of screening drugs for cancer therapy to identify suitable drugs for restoring BRCA1 gene product function.

Finally, the present invention provides the means necessary for production of gene-based therapies directed at cancer cells. These therapeutic agents may take the form of polynucleotides comprising all or a portion of the BRCA1 locus placed in appropriate vectors or delivered to target cells in more direct ways such that the function of the BRCA1 protein is reconstituted. Therapeutic agents may also take the form of polypeptides based on either a portion of, or the entire protein sequence of BRCA1. These may functionally replace the activity of BRCA1 in vivo.

It is a discovery of the present invention that the BRCA1 locus which predisposes individuals to breast cancer and ovarian cancer, is a gene encoding a BRCA1 protein, which has been found to have no significant homology with known protein or DNA sequences. This gene is termed BRCA1 herein. It is a discovery of the present invention that mutations in the BRCA1 locus in the germline are indicative of a predisposition to breast cancer and ovarian cancer. Finally, it is a discovery of the present invention that somatic mutations in the BRCA1 locus are also associated with breast cancer, ovarian cancer and other cancers, which represents an indicator of these cancers or of the prognosis of these cancers. The mutational events of the BRCA1 locus can involve deletions, insertions and point mutations within the coding sequence and the non-coding sequence.

Starting from a region on the long arm of human chromosome 17 of the human genome, 17q, which has a size estimated at about 8 million base pairs, a region which contains a genetic locus, BRCA1, which causes susceptibility to cancer, including breast and ovarian cancer, has been identified.

The region containing the BRCA1 locus was identified using a variety of genetic techniques. Genetic mapping techniques initially defined the BRCA1 region in terms of recombination with genetic markers. Based upon studies of large extended families ("kindreds") with multiple cases of breast cancer (and ovarian cancer cases in some kindreds), a chromosomal region has been pinpointed that contains the BRCA1 gene as well as other putative susceptibility alleles in the BRCA1 locus. Two meiotic breakpoints have been discovered on the distal side of the BRCA1 locus which are expressed as recombinants between genetic markers and the disease, and one recombinant on the proximal side of the BRCA1 locus. Thus, a region which contains the BRCA1 locus is physically bounded by these markers.

The use of the genetic markers provided by this invention allowed the identification of clones which cover the region from a human yeast artificial chromosome (YAC) or a human bacterial artificial chromosome (BAC) library. It also allowed for the identification and preparation of more easily manipulated cosmid, P1 and BAC clones from this region and the construction of a contig from a subset of the clones. These cosmids, P1s, YACs and BACs provide the basis for cloning the BRCA1 locus and provide the basis for developing reagents effective, for example, in the diagnosis and treatment of breast and/or ovarian cancer. The BRCA1 gene and other potential susceptibility genes have been isolated from this region. The isolation was done using software trapping (a computational method for identifying sequences likely to contain coding exons, from contiguous or discontinuous genomic DNA sequences), hybrid selection techniques and direct screening, with whole or partial cDNA inserts from cosmids, P1s and BACs, in the region to screen cDNA libraries. These methods were used to obtain sequences of loci expressed in breast and other tissue. These candidate loci were analyzed to identify sequences which confer cancer susceptibility. We have discovered that there are mutations in the coding sequence of the BRCA1 locus in kindreds which are responsible for the 17q-linked cancer susceptibility known as BRCA1. This gene was not known to be in this region. The present invention not only facilitates the early detection of certain cancers, so vital to patient survival, but also permits the detection of susceptible individuals before they develop cancer.

Population Resources

Large, well-documented Utah kindreds are especially important in providing good resources for human genetic studies. Each large kindred independently provides the power to detect whether a BRCA1 susceptibility allele is segregating in that family. Recombinants informative for localization and isolation of the BRCA1 locus could be obtained only from kindreds large enough to confirm the presence of a susceptibility allele. Large sibships are especially important for studying breast cancer, since penetrance of the BRCA1 susceptibility allele is reduced both by age and sex, making informative sibships difficult to find. Furthermore, large sibships are essential for constructing haplotypes of deceased individuals by inference from the haplotypes of their close relatives.

While other populations may also provide beneficial information, such studies generally require much greater effort, and the families are usually much smaller and thus less informative. Utah's age-adjusted breast cancer incidence is 20% lower than the average U.S. rate. The lower incidence in Utah is probably due largely to an early age at first pregnancy, increasing the probability that cases found in Utah kindreds carry a genetic predisposition.

Genetic Mapping

Given a set of informative families, genetic markers are essential for linking a disease to a region of a chromosome. Such markers include restriction fragment length polymorphisms (RFLPs) (Botstein et al., 1980), markers with a variable number of tandem repeats (VNTRs) (Jeffreys et al., 1985; Nakamura et al., 1987), and an abundant class of DNA polymorphisms based on short tandem repeats (STRs), especially repeats of CpA (Weber and May, 1989; Litt et al., 1989). To generate a genetic map, one selects potential genetic markers and tests them using DNA extracted from members of the kindreds being studied.

Genetic markers useful in searching for a genetic locus associated with a disease can be selected on an ad hoc basis, by densely covering a specific chromosome, or by detailed analysis of a specific region of a chromosome. A preferred method for selecting genetic markers linked with a disease involves evaluating the degree of informativeness of kindreds to determine the ideal distance between genetic markers of a given degree of polymorphism, then selecting markers from known genetic maps which are ideally spaced for maximal efficiency. Informativeness of kindreds is measured by the probability that the markers will be heterozygous in unrelated individuals. It is also most efficient to use STR markers which are detected by amplification of the target nucleic acid sequence using PCR; such markers are highly informative, easy to assay (Weber and May, 1989), and can be assayed simultaneously using multiplexing strategies (Skolnick and Wallace, 1988), greatly reducing the number of experiments required.

Once linkage has been established, one needs to find markers that flank the disease locus, i.e., one or more markers proximal to the disease locus, and one or more markers distal to the disease locus. Where possible, candidate markers can be selected from a known genetic map. Where none is known, new markers can be identified by the STR technique, as shown in the Examples.

Genetic mapping is usually an iterative process. In the present invention, it began by defining flanking genetic markers around the BRCA1 locus, then replacing these flanking markers with other markers that were successively closer to the BRCA1 locus. As an initial step, recombination events, defined by large extended kindreds, helped specifically to localize the BRCA1 locus as either distal or proximal to a specific genetic marker (Goldgar et al., 1994).

The region surrounding BRCA1, until the disclosure of the present invention, was not well mapped and there were few markers. Therefore, short repetitive sequences on cosmids subcloned from YACs, which had been physically mapped, were analyzed in order to develop new genetic markers. Using this approach, one marker of the present invention, 42D6, was discovered which replaced pCMM86 as the distal flanking marker for the BRCA1 region. Since 42D6 is approximately 14 cM from pCMM86, the BRCA1 region was thus reduced by approximately 14 centiMorgans (Easton et al., 1993). The present invention thus began by finding a much more closely linked distal flanking marker of the BRCA1 region. BRCA1 was then discovered to be distal to the genetic marker Mfd15. Therefore, BRCA1 was shown to be in a region of 6 to 10 million bases bounded by Mfd15 and 42D6. Marker Mfd191was subsequently discovered to be distal to Mfd15 and proximal to BRCA1. Thus, Mfd15 was replaced with Mfd191 as the closest proximal genetic marker. Similarly, it was discovered that genetic marker Mfd188 could replace genetic marker 42D6, narrowing the region containing the BRCA1 locus to approximately 1.5 million bases. Then the marker Mfd191 was replaced with tdj1474 as the proximal marker and Mfd188 was replaced with U5R as the distal marker, further narrowing the BRCA1 region to a small enough region to allow isolation and characterization of the BRCA1 locus (see FIG. 3), using techniques known in the art and described herein.

Physical Mapping

Three distinct methods were employed to physically map the region. The first was the use of yeast artificial chromosomes (YACs) to clone the region which is flanked by tdj1474 and U5R. The second was the creation of a set of P1, BAC and cosmid clones which cover the region containing the BRCA1 locus.

Yeast Artificial Chromosomes (YACs). Once a sufficiently small region containing the BRCA1 locus was identified, physical isolation of the DNA in the region proceeded by identifying a set of overlapping YACs which covers the region. Useful YACs can be isolated from known libraries, such as the St. Louis and CEPH YAC libraries, which are widely distributed and contain approximately 50,000 YACs each. The YACs isolated were from these publicly accessible libraries and can be obtained from a number of sources including the Michigan Genome Center. Clearly, others who had access to these YACs, without the disclosure of the present invention, would not have known the value of the specific YACs we selected since they would not have known which YACs were within, and which YACs outside of, the smallest region containing the BRCA1 locus.

Cosmid, P1 and BAC Clones. In the present invention, it is advantageous to proceed by obtaining cosmid, P1, and BAC clones to cover this region. The smaller size of these inserts, compared to YAC inserts, makes them more useful as specific hybridization probes. Furthermore, having the cloned DNA in bacterial cells, rather than in yeast cells, greatly increases the ease with which the DNA of interest can be manipulated, and improves the signal-to-noise ratio of hybridization assays. For cosmid subclones of YACs, the DNA is partially digested with the restriction enzyme Sau3A and cloned into the BamHI site of the pWE15 cosmid vector (Stratagene, cat. #1251201). The cosmids containing human sequences are screened by hybridization with human repetitive DNA (e.g., Gibco/BRL, Human C_ot-1 DNA, cat. 5279SA), and then fingerprinted by a variety of techniques, as detailed in the Examples.

P1 and BAC clones are obtained by screening libraries constructed from the total human genome with specific sequence tagged sites (STSs) derived from the YACs, cosmids or P1s and BACs, isolated as described herein.

These P1, BAC and cosmid clones can be compared by interspersed repetitive sequence (IRS) PCR and/or restriction enzyme digests followed by gel electrophoresis and comparison of the resulting DNA fragments ("fingerprints") (Maniatis et al., 1982). The clones can also be characterized by the presence of STSs. The fingerprints are used to define an overlapping contiguous set of clones which covers the region but is not excessively redundant, referred to herein as a "minimum tiling path". Such a minimum tiling path forms the basis for subsequent experiments to identify cDNAs which may originate from the BRCA1 locus.

Coverage of the Gap with P1 and BAC Clones. To cover any gaps in the BRCA1 contig between the identified cosmids with genomic clones, clones in P1 and BAC vectors which contain inserts of genomic DNA roughly twice as large as cosmids for P1s and still greater for BACs (Sternberg, 1990; Sternberg et al., 1990; Pierce et al., 1992; Shizuya et al., 1992) were used. P1 clones were isolated by Genome Sciences using PCR primers provided by us for screening. BACs were provided by hybridization techniques in Dr. Mel Simon's laboratory. The strategy of using P1 clones also permitted the covering of the genomic region with an independent set of clones not derived from YACs. This guards against the possibility of other deletions in YACs that have not been detected. These new sequences derived from the P1 clones provide the material for further screening for candidate genes, as described below.

Gene Isolation.

There are many techniques for testing genomic clones for the presence of sequences likely to be candidates for the coding sequence of a locus one is attempting to isolate, including but not limited to:

a. zoo blots

b. identifying HTF islands

c. exon trapping

d. hybridizing cDNA to cosmids or YACs.

e. screening cDNA libraries.

(a) Zoo blots. The first technique is to hybridize cosmids to Southern blots to identify DNA sequences which are evolutionarily conserved, and which therefore give positive hybridization signals with DNA from species of varying degrees of relationship to humans (such as monkey, cow, chicken, pig, mouse and rat). Southern blots containing such DNA from a variety of species are commercially available (Clonetech, Cat. 7753-1).

(b) Identifing HTF islands. The second technique involves finding regions rich in the nucleotides C and G, which often occur near or within coding sequences. Such sequences are called HTF (HpaI tiny fragment) or CpG islands, as restriction enzymes specific for sites which contain CpG dimers cut frequently in these regions (Lindsay et al., 1987).

(c) Exon trapping. The third technique is exon trapping, a method that identifies sequences in genomic DNA which contain splice junctions and therefore are likely to comprise coding sequences of genes. Exon amplification (Buckler et al., 1991) is used to select and amplify exons from DNA clones described above. Exon amplification is based on the selection of RNA sequences which are flanked by functional 5' and/or 3' splice sites. The products of the exon amplification are used to screen the breast cDNA libraries to identify a manageable number of candidate genes for further study. Exon trapping can also be performed on small segments of sequenced DNA using computer programs or by software trapping.

(d) Hybridizing cDNA to Cosmids, P1s, BACs or YACs. The fourth technique is a modification of the selective enrichment technique which utilizes hybridization of cDNA to cosmids, P1s, BACs or YACs and permits transcribed sequences to be identified in, and recovered from cloned genomic DNA (Kandpal et al. 1990). The selective enrichment technique, as modified for the present purpose, involves binding DNA from the region of BRCA1 present in a YAC to a column matrix and selecting cDNAs from the relevant libraries which hybridize with the bound DNA, followed by amplification and purification of the bound DNA, resulting in a great enrichment for cDNAs in the region represented by the cloned genomic DNA.

(e) Identification of cDNAs. The fifth technique is to identify cDNAs that correspond to the BRCA1 locus. Hybridization probes containing putative coding sequences, selected using any of the above techniques, are used to screen various libraries, including breast tissue cDNA libraries, ovarian cDNA libraries, and any other necessary libraries.

Another variation on the theme of direct selection of cDNA was also used to find candidate genes for BRCA1 (Lovett et al., 1991; Futreal, 1993). This method uses cosmid, P1 or BAC DNA as the probe. The probe DNA is digested with a blunt cutting restriction enzyme such as HaeIII. Double stranded adapters are then ligated onto the DNA and serve as binding sites for primers in subsequent PCR amplification reactions using biotinylated primers. Target cDNA is generated from mRNA derived from tissue samples, e.g., breast tissue, by synthesis of either random primed or oligo(dT) primed first strand followed by second strand synthesis. The cDNA ends are rendered blunt and ligated onto double-stranded adapters. These adapters serve as amplification sites for PCR. The target and probe sequences are denatured and mixed with human C_ot–1 DNA to block repetitive sequences.

Solution hybridization is carried out to high C_ot–½ values to ensure hybridization of rare target cDNA molecules. The annealed material is then captured on avidin beads, washed at high stringency and the retained cDNAs are eluted and amplified by PCR. The selected cDNA is subjected to further rounds of enrichment before cloning into a plasmid vector for analysis.

Testing the cDNA for Candidacy

Proof that the cDNA is the BRCA1 locus is obtained by finding sequences in DNA extracted from affected kindred members which create abnormal BRCA1 gene products or abnormal levels of BRCA1 gene product. Such BRCA1 susceptibility alleles will co-segregate with the disease in large kindreds. They will also be present at a much higher frequency in non-kindred individuals with breast and ovarian cancer then in individuals in the general population. Finally, since tumors often mutate somatically at loci which are in other instances mutated in the germline, we expect to see normal germline BRCA1 alleles mutated into sequences which are identical or similar to BRCA1 susceptibility alleles in DNA extracted from tumor tissue. Whether one is comparing BRCA1 sequences from tumor tissue to BRCA1 alleles from the germline of the same individuals, or one is comparing germline BRCA1 alleles from cancer cases to those from unaffected individuals, the key is to find mutations which are serious enough to cause obvious disruption to the normal function of the gene product. These mutations can take a number of forms. The most severe forms would be frame shift mutations or large deletions which would cause the gene to code for an abnormal protein or one which would significantly alter protein expression. Less severe disruptive mutations would include small in-frame deletions and nonconservative base pair substitutions which would have a significant effect on the protein produced, such as changes to or from a cysteine residue, from a basic to an acidic amino acid or vice versa, from a hydrophobic to hydrophilic amino acid or vice versa, or other mutations which would affect secondary, tertiary or quaternary protein structure. Silent mutations or those resulting in conservative amino acid substitutions would not generally be expected to disrupt protein function.

According to the diagnostic and prognostic method of the present invention, alteration of the wild-type BRCA1 locus is detected. In addition, the method can be performed by detecting the wild-type BRCA1 locus and confirming the lack of a predisposition to cancer at the BRCA1 locus. "Alteration of a wild-type gene" encompasses all forms of mutations including deletions, insertions and point mutations in the coding and noncoding regions. Deletions may be of the entire gene or of only a portion of the gene. Point mutations may result in stop codons, frameshift mutations or amino acid substitutions. Somatic mutations are those which occur only in certain tissues, e.g., in the tumor tissue, and are not inherited in the germline. Germline mutations can be found in any of a body's tissues and are inherited. If only a single allele is somatically mutated, an early neoplastic state is indicated. However, if both alleles are somatically mutated, then a late neoplastic state is indicated. The finding of BRCA1 mutations thus provides both diagnostic and prognostic information. A BRCA1 allele which is not deleted (e.g., found on the sister chromosome to a chromosome carrying a BRCA1 deletion) can be screened for other mutations, such as insertions, small deletions, and point mutations. It is believed that many mutations found in tumor tissues will be those leading to decreased expression of the BRCA1 gene product. However, mutations leading to nonfunctional gene products would also lead to a cancerous state. Point mutational events may occur in regulatory regions, such as in the promoter of the gene, leading to loss or diminution of expression of the mRNA. Point mutations may also abolish proper RNA processing, leading to loss of expression of the BRCA1 gene product, or to a decrease in mRNA stability or translation efficiency.

Useful diagnostic techniques include, but are not limited to fluorescent in situ hybridization (FISH), direct DNA sequencing, PFGE analysis, Southern blot analysis, single stranded conformation analysis (SSCA), RNase protection assay, allele-specific oligonucleotide (ASO), dot blot analysis and PCR-SSCP, as discussed in detail further below.

Predisposition to cancers, such as breast and ovarian cancer, and the other cancers identified herein, can be ascertained by testing any tissue of a human for mutations of the BRCA1 gene. For example, a person who has inherited a germline BRCA1 mutation would be prone to develop cancers. This can be determined by testing DNA from any tissue of the person's body. Most simply, blood can be drawn and DNA extracted from the cells of the blood. In addition, prenatal diagnosis can be accomplished by testing fetal cells, placental cells or amniotic cells for mutations of the BRCA1 gene. Alteration of a wild-type BRCA1 allele, whether, for example, by point mutation or deletion, can be detected by any of the means discussed herein.

There are several methods that can be used to detect DNA sequence variation. Direct DNA sequencing, either manual sequencing or automated fluorescent sequencing can detect sequence variation. For a gene as large as BRCA1, manual sequencing is very labor-intensive, but under optimal conditions, mutations in the coding sequence of a gene are rarely missed. Another approach is the single-stranded conformation polymorphism assay (SSCA) (Orita et al., 1989). This method does not detect all sequence changes, especially if the DNA fragment size is greater than 200 bp, but can be optimized to detect most DNA sequence variation. The reduced detection sensitivity is a disadvantage, but the increased throughput possible with SSCA makes it an attractive, viable alternative to direct sequencing for mutation detection on a research basis. The fragments which have shifted mobility on SSCA gels are then sequenced to determine the exact nature of the DNA sequence variation. Other approaches based on the detection of mismatches between the two complementary DNA strands include clamped denaturing gel electrophoresis (CDGE) (Sheffield et al., 1991), heteroduplex analysis (HA) (White et al., 1992) and chemical mismatch cleavage (CMC) (Grompe et al., 1989). None of the methods described above will detect large deletions, duplications or insertions, nor will they detect a regulatory mutation which affects transcription or translation of the protein. Other methods which might detect these classes of mutations such as a protein truncation assay or the asymmetric assay, detect only specific types of mutations and would not detect missense mutations. A review of currently available methods of detecting DNA sequence variation can be found in a recent review by Grompe (1993). Once a mutation is known, an allele specific detection approach such as allele specific oligonucleotide (ASO) hybridization can be utilized to rapidly screen large numbers of other samples for that same mutation.

In order to detect the alteration of the wild-type BRCA1 gene in a tissue, it is helpful to isolate the tissue free from surrounding normal tissues. Means for enriching tissue preparation for tumor cells are known in the art. For example, the tissue may be isolated from paraffin or cryostat sections. Cancer cells may also be separated from normal cells by flow cytometry. These techniques, as well as other techniques for separating tumor cells from normal cells, are well known in the art. If the tumor tissue is highly contaminated with normal cells, detection of mutations is more difficult.

A rapid preliminary analysis to detect polymorphisms in DNA sequences can be performed by looking at a series of Southern blots of DNA cut with one or more restriction enzymes, preferably with a large number of restriction enzymes. Each blot contains a series of normal individuals and a series of cancer cases, tumors, or both. Southern blots displaying hybridizing fragments (differing in length from control DNA when probed with sequences near or including the BRCA1 locus) indicate a possible mutation. If restriction enzymes which produce very large restriction fragments are used, then pulsed field gel electrophoresis (PFGE) is employed.

Detection of point mutations may be accomplished by molecular cloning of the BRCA1 allele(s) and sequencing the allele(s) using techniques well known in the art. Alternatively, the gene sequences can be amplified directly from a genomic DNA preparation from the tumor tissue, using known techniques. The DNA sequence of the amplified sequences can then be determined.

There are six well known methods for a more complete, yet still indirect, test for confirming the presence of a susceptibility allele: 1) single stranded conformation analysis (SSCA) (Orita et al., 1989); 2) denaturing gradient gel electrophoresis (DGGE) (Wartell et al., 1990; Sheffield et al., 1989); 3) RNase protection assays (Finkelstein et al., 1990; Kinszler et al., 1991); 4) allele-specific oligonucleotides (ASOs) (Conner et al., 1983); 5) the use of proteins which recognize nucleotide mismatches, such as the *E. coli* mutS protein (Modrich, 1991); and 6) allele-specific PCR (Rano & Kidd, 1989). For allele-specific PCR, primers are used which hybridize at their 3' ends to a particular BRCA1 mutation. If the particular BRCA1 mutation is not present, an amplification product is not observed. Amplification Refractory Mutation System (ARMS) can also be used, as disclosed in European Patent Application Publication No. 0332435 and in Newton et al., 1989. Insertions and deletions of genes can also be detected by cloning, sequencing and amplification. In addition, restriction fragment length polymorphism (RFLP) probes for the gene or surrounding marker genes can be used to score alteration of an allele or an insertion in a polymorphic fragment. Such a method is particularly useful for screening relatives of an affected individual for the presence of the BRCA1 mutation found in that individual. Other techniques for detecting insertions and deletions as known in the art can be used.

In the first three methods (SSCA, DGGE and RNase protection assay), a new electrophoretic band appears. SSCA detects a band which migrates differentially because the sequence change causes a difference in single-strand, intramolecular base pairing. RNase protection involves cleavage of the mutant polynucleotide into two or more smaller fragments. DGGE detects differences in migration rates of mutant sequences compared to wild-type sequences, using a denaturing gradient gel. In an allele-specific oligonucleotide assay, an oligonucleotide is designed which detects a specific sequence, and the assay is performed by detecting the presence or absence of a hybridization signal. In the mutS assay, the protein binds only to sequences that contain a nucleotide mismatch in a heteroduplex between mutant and wild-type sequences.

Mismatches, according to the present invention, are hybridized nucleic acid duplexes in which the two strands are not 100% complementary. Lack of total homology may be due to deletions, insertions, inversions or substitutions. Mismatch detection can be used to detect point mutations in the gene or in its mRNA product. While these techniques are less sensitive than sequencing, they are simpler to perform on a large number of tumor samples. An example of a mismatch cleavage technique is the RNase protection method. In the practice of the present invention, the method involves the use of a labeled riboprobe which is complementary to the human wild-type BRCA1 gene coding sequence. The riboprobe and either mRNA or DNA isolated from the tumor tissue are annealed (hybridized) together and subsequently digested with the enzyme RNase A which is able to detect some mismatches in a duplex RNA structure. If a mismatch is detected by RNase A, it cleaves at the site of the mismatch. Thus, when the annealed RNA preparation is separated on an electrophoretic gel matrix, if a mismatch has been detected and cleaved by RNase A, an RNA product will be seen which is smaller than the full length duplex RNA for the riboprobe and the mRNA or DNA. The riboprobe need not be the full length of the BRCA1 mRNA or gene but can be a segment of either. If the riboprobe comprises only a segment of the BRCA1 mRNA or gene, it will be desirable to use a number of these probes to screen the whole mRNA sequence for mismatches.

In similar fashion, DNA probes can be used to detect mismatches, through enzymatic or chemical cleavage. See, e.g., Cotton et al., 1988; Shenk et al., 1975; Novack et al., 1986. Alternatively, mismatches can be detected by shifts in the electrophoretic mobility of mismatched duplexes relative to matched duplexes. See, e.g., Cariello, 1988. With either riboprobes or DNA probes, the cellular mRNA or DNA which might contain a mutation can be amplified using PCR (see below) before hybridization. Changes in DNA of the BRCA1 gene can also be detected using Southern hybridization, especially if the changes are gross rearrangements, such as deletions and insertions.

DNA sequences of the BRCA1 gene which have been amplified by use of PCR may also be screened using allele-specific probes. These probes are nucleic acid oligomers, each of which contains a region of the BRCA1 gene sequence harboring a known mutation. For example, one oligomer may be about 30 nucleotides in length, corresponding to a portion of the BRCA1 gene sequence. By use of a battery of such allele-specific probes, PCR amplification products can be screened to identify the presence of a previously identified mutation in the BRCA1 gene. Hybridization of allele-specific probes with amplified BRCA1 sequences can be performed, for example, on a nylon filter. Hybridization to a particular probe under stringent hybridization conditions indicates the presence of the same mutation in the tumor tissue as in the allele-specific probe.

The most definitive test for mutations in a candidate locus is to directly compare genomic BRCA1 sequences from cancer patients with those from a control population. Alternatively, one could sequence messenger RNA after amplification, e.g., by PCR, thereby eliminating the necessity of determining the exon structure of the candidate gene.

Mutations from cancer patients falling outside the coding region of BRCA1 can be detected by examining the non-coding regions, such as introns and regulatory sequences near or within the BRCA1 gene. An early indication that mutations in noncoding regions are important may come from Northern blot experiments that reveal messenger RNA molecules of abnormal size or abundance in cancer patients as compared to control individuals.

Alteration of BRCA1 mRNA expression can be detected by any techniques known in the art. These include Northern blot analysis, PCR amplification and RNase protection. Diminished mRNA expression indicates an alteration of the wild-type BRCA1 gene. Alteration of wild-type BRCA1 genes can also be detected by screening for alteration of wild-type BRCA1 protein. For example, monoclonal antibodies immunoreactive with BRCA1 can be used to screen a tissue. Lack of cognate antigen would indicate a BRCA1 mutation. Antibodies specific for products of mutant alleles could also be used to detect mutant BRCA1 gene product. Such immunological assays can be done in any convenient formats known in the art. These include Western blots, immunohistochemical assays and ELISA assays. Any means for detecting an altered BRCA1 protein can be used to detect alteration of wild-type BRCA1 genes. Functional assays, such as protein binding determinations, can be used. In addition, assays can be used which detect BRCA1 biochemical function. Finding a mutant BRCA1 gene product indicates alteration of a wild-type BRCA1 gene.

Mutant BRCA1 genes or gene products can also be detected in other human body samples, such as serum, stool, urine and sputum. The same techniques discussed above for detection of mutant BRCA1 genes or gene products in tissues can be applied to other body samples. Cancer cells are sloughed off from tumors and appear in such body samples. In addition, the BRCA1 gene product itself may be secreted into the extracellular space and found in these body samples even in the absence of cancer cells. By screening such body samples, a simple early diagnosis can be achieved for many types of cancers. In addition, the progress of chemotherapy or radiotherapy can be monitored more easily by testing such body samples for mutant BRCA1 genes or gene products.

The methods of diagnosis of the present invention are applicable to any tumor in which BRCA1 has a role in tumorigenesis. The diagnostic method of the present invention is useful for clinicians, so they can decide upon an appropriate course of treatment.

The primer pairs of the present invention are useful for determination of the nucleotide sequence of a particular BRCA1 allele using PCR. The pairs of single-stranded DNA primers can be annealed to sequences within or surrounding the BRCA1 gene on chromosome 17q21 in order to prime amplifying DNA synthesis of the BRCA1 gene itself. A complete set of these primers allows synthesis of all of the nucleotides of the BRCA1 gene coding sequences, i.e., the exons. The set of primers preferably allows synthesis of both intron and exon sequences. Allele-specific primers can also be used. Such primers anneal only to particular BRCA1 mutant alleles, and thus will only amplify a product in the presence of the mutant allele as a template.

In order to facilitate subsequent cloning of amplified sequences, primers may have restriction enzyme site sequences appended to their 5' ends. Thus, all nucleotides of the primers are derived from BRCA1 sequences or sequences adjacent to BRCA1, except for the few nucleotides necessary to form a restriction enzyme site. Such enzymes and sites are well known in the art. The primers themselves can be synthesized using techniques which are well known in the art. Generally, the primers can be made using oligonucleotide synthesizing machines which are commercially available. Given the sequence of the BRCA1 open reading frame shown in SEQ ID NO: 1, design of particular primers is well within the skill of the art.

The nucleic acid probes provided by the present invention are useful for a number of purposes. They can be used in Southern hybridization to genomic DNA and in the RNase protection method for detecting point mutations already discussed above. The probes can be used to detect PCR amplification products. They may also be used to detect mismatches with the BRCA1 gene or mRNA using other techniques.

It has been discovered that individuals with the wild-type BRCA1 gene do not have cancer which results from the BRCA1 allele. However, mutations which interfere with the function of the BRCA1 protein are involved in the pathogenesis of cancer. Thus, the presence of an altered (or a mutant) BRCA1 gene which produces a protein having a loss of function, or altered function, directly correlates to an increased risk of cancer. In order to detect a BRCA1 gene mutation, a biological sample is prepared and analyzed for a difference between the sequence of the BRCA1 allele being analyzed and the sequence of the wild-type BRCA1 allele. Mutant BRCA1 alleles can be initially identified by any of the techniques described above. The mutant alleles are then sequenced to identify the specific mutation of the particular mutant allele. Alternatively, mutant BRCA1 alleles can be initially identified by identifying mutant (altered) BRCA1 proteins, using conventional techniques. The mutant alleles are then sequenced to identify the specific mutation for each allele. The mutations, especially those which lead to an altered function of the BRCA1 protein, are then used for the diagnostic and prognostic methods of the present invention.

DEFINITIONS

The present invention employs the following definitions:

"Amplification of Polynucleotides" utilizes methods such as the polymerase chain reaction (PCR), ligation amplification (or ligase chain reaction, LCR) and amplification methods based on the use of Q-beta replicase. These methods are well known and widely practiced in the art. See, e.g., U.S. Pat. Nos. 4,683,195 and 4,683,202 and Innis et al., 1990 (for PCR); and Wu et al., 1989a (for LCR). Reagents and hardware for conducting PCR are commercially available. Primers useful to amplify sequences from the BRCA1 region are preferably complementary to, and hybridize specifically to sequences in the BRCA1 region or in regions that flank a target region therein. BRCA1 sequences generated by amplification may be sequenced directly. Alternatively, but less desirably, the amplified sequence(s) may be cloned prior to sequence analysis. A method for the direct cloning and sequence analysis of enzymatically amplified genomic segments has been described by Scharf, 1986.

"Analyte polynucleotide" and "analyte strand" refer to a single- or double-stranded polynucleotide which is suspected of containing a target sequence, and which may be present in a variety of types of samples, including biological samples.

"Antibodies." The present invention also provides polyclonal and/or monoclonal antibodies and fragments thereof, and immunologic binding equivalents thereof, which are capable of specifically binding to the BRCA1 polypeptides and fragments thereof or to polynucleotide sequences from the BRCA1 region, particularly from the BRCA1 locus or a portion thereof. The term "antibody" is used both to refer to a homogeneous molecular entity, or a mixture such as a serum product made up of a plurality of different molecular entities. Polypeptides may be prepared synthetically in a peptide synthesizer and coupled to a carrier molecule (e.g., keyhole limpet hemocyanin) and injected over several months into rabbits. Rabbit sera is tested for immunoreactivity to the BRCA1 polypeptide or fragment. Monoclonal antibodies may be made by injecting mice with the protein polypeptides, fusion proteins or fragments thereof. Monoclonal antibodies will be screened by ELISA and tested for specific immunoreactivity with BRCA1 polypeptide or fragments thereof. See, Harlow & Lane, 1988. These antibodies will be useful in assays as well as pharmaceuticals.

Once a sufficient quantity of desired polypeptide has been obtained, it may be used for various purposes. A typical use is the production of antibodies specific for binding. These antibodies may be either polyclonal or monoclonal, and may be produced by in vitro or in vivo techniques well known in the art. For production of polyclonal antibodies, an appropriate target immune system, typically mouse or rabbit, is selected. Substantially purified antigen is presented to the immune system in a fashion determined by methods appropriate for the animal and by other parameters well known to immunologists. Typical sites for injection are in footpads, intramuscularly, intraperitoneally, or intradermally. Of course, other species may be substituted for mouse or rabbit. Polyclonal antibodies are then purified using techniques known in the art, adjusted for the desired specificity.

An immunological response is usually assayed with an immunoassay. Normally, such immunoassays involve some purification of a source of antigen, for example, that produced by the same cells and in the same fashion as the antigen. A variety of immunoassay methods are well known in the art. See, e.g., Harlow & Lane, 1988, or Goding, 1986.

Monoclonal antibodies with affinities of 10^{-8} M^{-1} or preferably 10^{-9} to 10^{-10} M^{-1} or stronger will typically be made by standard procedures as described, e.g., in Harlow & Lane, 1988 or Goding, 1986. Briefly, appropriate animals will be selected and the desired immunization protocol followed. After the appropriate period of time, the spleens of such animals are excised and individual spleen cells fused, typically, to immortalized myeloma cells under appropriate selection conditions. Thereafter, the cells are clonally separated and the supernatants of each clone tested for their production of an appropriate antibody specific for the desired region of the antigen.

Other suitable techniques involve in vitro exposure of lymphocytes to the antigenic polypeptides, or alternatively, to selection of libraries of antibodies in phage or similar vectors. See Huse et al., 1989. The polypeptides and antibodies of the present invention may be used with or without modification. Frequently, polypeptides and antibodies will be labeled by joining, either covalently or non-covalently, a substance which provides for a detectable signal. A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent agents, chemiluminescent agents, magnetic particles and the like. Patents teaching the use of such labels include U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149 and 4,366,241. Also, recombinant immunoglobulins may be produced (see U.S. Pat. No. 4,816,567).

"Binding partner" refers to a molecule capable of binding a ligand molecule with high specificity, as for example, an antigen and an antigen-specific antibody or an enzyme and its inhibitor. In general, the specific binding partners must bind with sufficient affinity to immobilize the analyte copy/complementary strand duplex (in the case of polynucleotide hybridization) under the isolation conditions. Specific binding partners are known in the art and include, for example, biotin and avidin or streptavidin, IgG and protein A, the numerous, known receptor-ligand couples, and complementary polynucleotide strands. In the case of complementary polynucleotide binding partners, the partners are normally at least about 15 bases in length, and may be at least 40 bases in length. The polynucleotides may be composed of DNA, RNA, or synthetic nucleotide analogs.

A "biological sample" refers to a sample of tissue or fluid suspected of containing an analyte polynucleotide or polypeptide from an individual including, but not limited to, e.g., plasma, serum, spinal fluid, lymph fluid, the external sections of the skin, respiratory, intestinal, and genitourinary tracts, tears, saliva, blood cells, tumors, organs, tissue and samples of in vitro cell culture constituents.

As used herein, the terms "diagnosing" or "prognosing," as used in the context of neoplasia, are used to indicate 1) the classification of lesions as neoplasia, 2) the determination of the severity of the neoplasia, or 3) the monitoring of the disease progression, prior to, during and after treatment.

"Encode". A polynucleotide is said to "encode" a polypeptide if, in its native state or when manipulated by methods well known to those skilled in the art, it can be transcribed and/or translated to produce the mRNA for and/or the polypeptide or a fragment thereof. The anti-sense strand is the complement of such a nucleic acid, and the encoding sequence can be deduced therefrom.

"Isolated" or "substantially pure". An "isolated" or "substantially pure" nucleic acid (e.g., an RNA, DNA or a mixed polymer) is one which is substantially seperated from other cellular components which naturally accompany a native human sequence or protein, e.g., ribosomes, polymerases, many other human genome sequences and proteins. The term embraces a nucleic acid sequence or protein which has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems.

"BRCA1 Allele" refers to normal alleles of the BRCA1 locus as well as alleles carrying variations that predispose individuals to develop cancer of many sites including, for example, breast, ovarian, colorectal and prostate cancer. Such predisposing alleles are also called "BRCA1 susceptibility alleles".

"BRCA1 Locus," "BRCA1 Gene," "BRCA1 Nucleic Acids" or "BRCA1 Polynucleotide" each refer to polynucleotides, all of which are in the BRCA1 region, that are likely to be expressed in normal tissue, certain alleles of which predispose an individual to develop breast, ovarian, colorectal and prostate cancers. Mutations at the BRCA1 locus may be involved in the initiation and/or progression of other types of tumors. The locus is indicated in part by mutations that predispose individuals to develop cancer. These mutations fall within the BRCA1 region described infra. The BRCA1 locus is intended to include coding sequences, intervening sequences and regulatory elements controlling transcription and/or translation. The BRCA1 locus is intended to include all allelic variations of the DNA sequence.

These terms, when applied to a nucleic acid, refer to a nucleic acid which encodes a BRCA1 polypeptide, fragment, homolog or variant, including, e.g., protein fusions or deletions. The nucleic acids of the present invention will possess a sequence which is either derived from, or substantially similar to a natural BRCA1-encoding gene or one having substantial homology with a natural BRCA1-encoding gene or a portion thereof. The coding sequence for a BRCA1 polypeptide is shown in SEQ ID NO:1, with the amino acid sequence shown in SEQ ID NO:2.

The polynucleotide compositions of this invention include RNA, cDNA, genomic DNA, synthetic forms, and mixed polymers, both sense and antisense strands, and may be chemically or biochemically modified or may contain non-natural or derivatized nucleotide bases, as will be readily appreciated by those skilled in the art. Such modifications include, for example, labels, methylation, substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoamidates, carbamates, etc.), charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), pendent moieties (e.g., polypeptides), intercalators (e.g., acridine, psoralen, etc.), chelators, alkylators, and modified linkages (e.g., alpha anomeric nucleic acids, etc.). Also included are synthetic molecules that mimic polynucleotides in their ability to bind to a designated sequence via hydrogen bonding and other chemical interactions. Such molecules are known in the art and include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule.

The present invention provides recombinant nucleic acids comprising all or part of the BRCA1 region. The recombinant construct may be capable of replicating autonomously in a host cell. Alternatively, the recombinant construct may become integrated into the chromosomal DNA of the host cell. Such a recombinant polynucleotide comprises a polynucleotide of genomic, cDNA, semi-synthetic, or synthetic origin which, by virtue of its origin or manipulation, 1) is not associated with all or a portion of a polynucleotide with which it is associated in nature; 2) is linked to a polynucleotide other than that to which it is linked in nature; or 3) does not occur in nature.

Therefore, recombinant nucleic acids comprising sequences otherwise not naturally occurring are provided by this invention. Although the wild-type sequence may be employed, it will often be altered, e.g., by deletion, substitution or insertion.

cDNA or genomic libraries of various types may be screened as natural sources of the nucleic acids of the present invention, or such nucleic acids may be provided by amplification of sequences resident in genomic DNA or other natural sources, e.g., by PCR. The choice of cDNA libraries normally corresponds to a tissue source which is abundant in mRNA for the desired proteins. Phage libraries are normally preferred, but other types of libraries may be used. Clones of a library are spread onto plates, transferred to a substrate for screening, denatured and probed for the presence of desired sequences.

The DNA sequences used in this invention will usually comprise at least about five codons (15 nucleotides), more usually at least about 7–15 codons, and most preferably, at least about 35 codons. One or more introns may also be present. This number of nucleotides is usually about the minimal length required for a successful probe that would hybridize specifically with a BRCA1-encoding sequence.

Techniques for nucleic acid manipulation are described generally, for example, in Sambrook et al., 1989 or Ausubel et al., 1992. Reagents useful in applying such techniques, such as restriction enzymes and the like, are widely known in the art and commercially available from such vendors as New England BioLabs, Boehringer Mannheim, Amersham, Promega Biotec, U. S. Biochemicals, New England Nuclear, and a number of other sources. The recombinant nucleic acid sequences used to produce fusion proteins of the present invention may be derived from natural or synthetic sequences. Many natural gene sequences are obtainable from various cDNA or from genomic libraries using appropriate probes. See, GenBank, National Institutes of Health.

"BRCA1 Region" refers to a portion of human chromosome 17q21 bounded by the markers tdj1474 and U5R. This region contains the BRCA1 locus, including the BRCA1 gene.

As used herein, the terms "BRCA1 locus," "BRCA1 allele" and "BRCA1 region" all refer to the double-stranded DNA comprising the locus, allele, or region, as well as either of the single-stranded DNAs comprising the locus, allele or region.

As used herein, a "portion" of the BRCA1 locus or region or allele is defined as having a minimal size of at least about eight nucleotides, or preferably about 15 nucleotides, or more preferably at least about 25 nucleotides, and may have a minimal size of at least about 40 nucleotides.

"BRCA1 protein" or "BRCA1 polypeptide" refer to a protein or polypeptide encoded by the BRCA1 locus, variants or fragments thereof. The term "polypeptide" refers to a polymer of amino acids and its equivalent and does not refer to a specific length of the product; thus, peptides, oligopeptides and proteins are included within the definition of a polypeptide. This term also does not refer to, or exclude modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations, and the like. Included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), polypeptides with substituted linkages as well as other modifications known in the art, both naturally and non-naturally occurring. Ordinarily, such polypeptides will be at least about 50% homologous to the native BRCA1 sequence, preferably in excess of about 90%, and more preferably at least about 95% homologous. Also included are proteins encoded by DNA which hybridize under high or low stringency conditions, to BRCA1-encoding nucleic acids and closely related polypeptides or proteins retrieved by antisera to the BRCA1 protein (s).

The length of polypeptide sequences compared for homology will generally be at least about 16 amino acids, usually at least about 20 residues, more usually at least about 24 residues, typically at least about 28 residues, and preferably more than about 35 residues.

"Operably linked" refers to a juxtaposition wherein the components so described are in a relationship permitting them to function in their intended manner. For instance, a promoter is operably linked to a coding sequence if the promoter affects its transcription or expression.

"Probes". Polynucleotide polymorphisms associated with BRCA1 alleles which predispose to certain cancers or are associated with most cancers are detected by hybridization with a polynucleotide probe which forms a stable hybrid with that of the target sequence, under stringent to moderately stringent hybridization and wash conditions. If it is expected that the probes will be perfectly complementary to the target sequence, stringent conditions will be used. Hybridization stringency may be lessened if some mismatching is expected, for example, if variants are expected with the result that the probe will not be completely complementary. Conditions are chosen which rule out nonspecific/adventitious bindings, that is, which minimize noise. Since such indications identify neutral DNA polymorphisms as well as mutations, these indications need further analysis to demonstrate detection of a BRCA1 susceptibility allele.

Probes for BRCA1 alleles may be derived from the sequences of the BRCA1 region or its cDNAs. The probes may be of any suitable length, which span all or a portion of the BRCA1 region, and which allow specific hybridization to the BRCA1 region. If the target sequence contains a sequence identical to that of the probe, the probes may be short, e.g., in the range of about 8–30 base pairs, since the hybrid will be relatively stable under even stringent conditions. If some degree of mismatch is expected with the probe, i.e., if it is suspected that the probe will hybridize to a variant region, a longer probe may be employed which hybridizes to the target sequence with the requisite specificity.

The probes will include an isolated polynucleotide attached to a label or reporter molecule and may be used to isolate other polynucleotide sequences, having sequence similarity by standard methods. For techniques for preparing and labeling probes see, e.g., Sambrook et al., 1989 or Ausubel et al., 1992. Other similar polynucleotides may be selected by using homologous polynucleotides. Alternatively, polynucleotides encoding these or similar polypeptides may be synthesized or selected by use of the redundancy in the genetic code. Various codon substitutions may be introduced, e.g., by silent changes (thereby producing various restriction sites) or to optimize expression for a particular system. Mutations may be introduced to modify the properties of the polypeptide, perhaps to change ligand-binding affinities, interchain affinities, or the polypeptide degradation or turnover rate.

Probes comprising synthetic oligonucleotides or other polynucleotides of the present invention may be derived from naturally occurring or recombinant single- or double-stranded polynucleotides, or be chemically synthesized. Probes may also be labeled by nick translation, Klenow fill-in reaction, or other methods known in the art.

Portions of the polynucleotide sequence having at least about eight nucleotides, usually at least about 15 nucleotides, and fewer than about 6 kb, usually fewer than about 1.0 kb, from a polynucleotide sequence encoding BRCA1 are preferred as probes. The probes may also be used to determine whether mRNA encoding BRCA1 is present in a cell or tissue.

"Protein modifications or fragments" are provided by the present invention for BRCA1 poly-peptides or fragments thereof which are substantially homologous to primary structural sequence but which include, e.g., in vivo or in vitro chemical and biochemical modifications or which incorporate unusual amino acids. Such modifications include, for example, acetylation, carboxylation, phospholylation, glycosylation, ubiquitination, labeling, e.g., with radionuclides, and various enzymatic modifications, as will be readily appreciated by those well skilled in the art. A variety of methods for labeling polypeptides and of substituents or labels useful for such purposes are well known in the art, and include radioactive isotopes such as ^{32}P, ligands which bind to labeled antiligands (e.g., antibodies), fluorophores, chemiluminescent agents, enzymes, and antiligands which can serve as specific binding pair members for a labeled ligand. The choice of label depends on the sensitivity required, ease of conjugation with the primer, stability requirements, and available instrumentation. Methods of labeling polypeptides are well known in the art. See, e.g., Sambrook et al., 1989 or Ausubel et al., 1992.

Besides substantially full-length polypeptides, the present invention provides for biologically active fragments of the polypeptides. Significant biological activities include ligand-binding, immunological activity and other biological activities characteristic of BRCA1 polypeptides. Immunological activities include both immunogenic function in a target immune system, as well as sharing of immunological epitopes for binding, serving as either a competitor or substitute antigen for an epitope of the BRCA1 protein. As used herein, "epitope" refers to an antigenic determinant of a polypeptide. An epitope could comprise three amino acids in a spatial conformation which is unique to the epitope. Generally, an epitope consists of at least five such amino acids, and more usually consists of at least 8–10 such amino acids. Methods of determining the spatial conformation of such amino acids are known in the art.

For immunological purposes, tandem-repeat polypeptide segments may be used as immunogens, thereby producing highly antigenic proteins. Alternatively, such polypeptides will serve as highly efficient competitors for specific binding. Production of antibodies specific for BRCA1 polypeptides or fragments thereof is described below.

The present invention also provides for fusion polypeptides, comprising BRCA1 polypeptides and fragments. Homologous polypeptides may be fusions between two or more BRCA1 polypeptide sequences or between the sequences of BRCA1 and a related protein. Likewise, heterologous fusions may be constructed which would exhibit a combination of properties or activities of the derivative proteins. For example, ligand-binding or other domains may be "swapped" between different new fusion polypeptides or fragments. Such homologous or heterologous fusion polypeptides may display, for example, altered strength or specificity of binding. Fusion partners include immunoglobulins, bacterial β-galactosidase, trpE, protein A, β-lactamase, alpha amylase, alcohol dehydrogenase and yeast alpha mating factor. See, e.g., Godowski et al., 1988.

Fusion proteins will typically be made by either recombinant nucleic acid methods, as described below, or may be chemically synthesized. Techniques for the synthesis of polypeptides are described, for example, in Merrifield, 1963.

"Protein purification" refers to various methods for the isolation of the BRCA1 polypeptides from other biological material, such as from cells transformed with recombinant nucleic acids encoding BRCA1, and are well known in the art. For example, such polypeptides may be purified by immunoaffinity chromatography employing, e.g., the antibodies provided by the present invention. Various methods of protein purification are well known in the art, and include those described in Deutscher, 1990 and Scopes, 1982.

The terms "isolated", "substantially pure", and "substantially homogeneous" are used interchangeably to describe a protein or polypeptide which has been separated from components which accompany it in its natural state. A monomeric protein is substantially pure when at least about 60 to 75% of a sample exhibits a single polypeptide sequence. A substantially pure protein will typically comprise about 60 to 90% W/W of a protein sample, more usually about 95%, and preferably will be over about 99% pure. Protein purity or homogeneity may be indicated by a number of means well known in the art, such as polyacrylamide gel electrophoresis of a protein sample, followed by visualizing a single polypeptide band upon staining the gel. For certain purposes, higher resolution may be provided by using HPLC or other means well known in the art which are utilized for purification.

A BRCA1 protein is substantially free of naturally associated components when it is separated from the native contaminants which accompany it in its natural state. Thus, a polypeptide which is chemically synthesized or synthesized in a cellular system different from the cell from which it naturally originates will be substantially free from its naturally associated components. A protein may also be rendered substantially free of naturally associated components by isolation, using protein purification techniques well known in the art.

A polypeptide produced as an expression product of an isolated and manipulated genetic sequence is an "isolated polypeptide," as used herein, even if expressed in a homologous cell type. Synthetically made forms or molecules expressed by heterologous cells are inherently isolated molecules.

"Recombinant nucleic acid" is a nucleic acid which is not naturally occurring, or which is made by the artificial combination of two otherwise separated segments of sequence. This artificial combination is often accomplished by either chemical synthesis means, or by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques. Such is usually done to replace a codon with a redundant codon encoding the same or a conservative amino acid, while typically introducing or removing a sequence recognition site. Alternatively, it is performed to join together nucleic acid segments of desired functions to generate a desired combination of functions.

"Regulatory sequences" refers to those sequences normally within 100 kb of the coding region of a locus, but they may also be more distant from the coding region, which affect the expression of the gene (including transcription of the gene, and translation, splicing, stability or the like of the messenger RNA).

"Substantial homology or similarity". A nucleic acid or fragment thereof is "substantially homologous" ("or substantially similar") to another if, when optimally aligned (with appropriate nucleotide insertions or deletions) with the other nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 60% of the nucleotide bases, usually at least about 70%, more usually at least about 80%, preferably at least about 90%, and more preferably at least about 95–98% of the nucleotide bases.

Alternatively, substantial homology or (similarity) exists when a nucleic acid or fragment thereof will hybridize to another nucleic acid (or a complementary strand thereof) under selective hybridization conditions, to a strand, or to its complement. Selectivity of hybridization exists when hybridization which is substantially more selective than total lack of specificity occurs. Typically, selective hybridization will occur when there is at least about 55% homology over a stretch of at least about 14 nucleotides, preferably at least about 65%, more preferably at least about 75%, and most preferably at least about 90%. See, Kanehisa, 1984. The length of homology comparison, as described, may be over longer stretches, and in certain embodiments will often be over a stretch of at least about nine nucleotides, usually at least about 20 nucleotides, more usually at least about 24 nucleotides, typically at least about 28 nucleotides, more typically at least about 32 nucleotides, and preferably at least about 36 or more nucleotides.

Nucleic acid hybridization will be affected by such conditions as salt concentration, temperature, or organic solvents, in addition to the base composition, length of the complementary strands, and the number of nucleotide base mismatches between the hybridizing nucleic acids, as will be readily appreciated by those skilled in the art. Stringent temperature conditions will generally include temperatures in excess of 30° C., typically in excess of 37° C. and preferably in excess of 45° C. Stringent salt conditions will ordinarily be less than 1000 mM, typically less than 500 mM, and preferably less than 200 mM. However, the combination of parameters is much more important than the measure of any single parameter. See, e.g., Wetmur & Davidson, 1968.

Probe sequences may also hybridize specifically to duplex DNA under certain conditions to form triplex or other higher order DNA complexes. The preparation of such probes and suitable hybridization conditions are well known in the art.

The terms "substantial homology" or "substantial identity", when referring to polypeptides, indicate that the polypeptide or protein in question exhibits at least about 30% identity with an entire naturally-occurring protein or a portion thereof, usually at least about 70% identity, and preferably at least about 95% identity.

"Substantially similar function" refers to the function of a modified nucleic acid or a modified protein, with reference to the wild-type BRCA1 nucleic acid or wild-type BRCA1 polypeptide. The modified polypeptide will be substantially homologous to the wild-type BRCA1 polypeptide and will have substantially the same function. The modified polypeptide may have an altered amino acid sequence and/or may contain modified amino acids. In addition to the similarity of function, the modified polypeptide may have other useful properties, such as a longer half-life. The similarity of function (activity) of the modified polypeptide may be substantially the same as the activity of the wild-type BRCA1 polypeptide. Alternatively, the similarity of function (activity) of the modified polypeptide may be higher than the activity of the wild-type BRCA1 polypeptide. The modified poly-peptide is synthesized using conventional techniques, or is encoded by a modified nucleic acid and produced using conventional techniques. The modified nucleic acid is prepared by conventional techniques. A nucleic acid with a function substantially similar to the wild-type BRCA1 gene function produces the modified protein described above.

Homology, for polypeptides, is typically measured using sequence analysis software. See, e.g., the Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 910 University Avenue, Madison, Wisc. 53705. Protein analysis software matches similar sequences using measure of homology assigned to various substitutions, deletions and other modifications. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine.

A polypeptide "fragment," "portion" or "segment" is a stretch of amino acid residues of at least about five to seven contiguous amino acids, often at least about seven to nine contiguous amino acids, typically at least about nine to 13 contiguous amino acids and, most preferably, at least about 20 to 30 or more contiguous amino acids.

The polypeptides of the present invention, if soluble, may be coupled to a solid-phase support, e.g., nitrocellulose, nylon, column packing materials (e.g., Sepharose beads), magnetic beads, glass wool, plastic, metal, polymer gels, cells, or other substrates. Such supports may take the form, for example, of beads, wells, dipsticks, or membranes.

"Target region" refers to a region of the nucleic acid which is amplified and/or detected. The term "target sequence" refers to a sequence with which a probe or primer will form a stable hybrid under desired conditions.

The practice of the present invention employs, unless otherwise indicated, conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA, genetics, and immunology. See, e.g., Maniatis et al., 1982; Sambrook et al., 1989; Ausubel et al., 1992; Glover, 1985; Anand, 1992; Guthrie & Fink, 1991. A general discussion of techniques and materials for human gene mapping, including mapping of human chromosome 17q, is provided, e.g., in White and Lalouel, 1988.

Preparation of Recombinant or Chemically Synthesized Nucleic Acids; Vectors, Transformation, Host Cells

Large amounts of the polynucleotides of the present invention may be produced by replication in a suitable host cell. Natural or synthetic polynucleotide fragments coding for a desired fragment will be incorporated into recombinant polynucleotide constructs, usually DNA constructs, capable of introduction into and replication in a prokaryotic or eukaryotic cell. Usually the polynucleotide constructs will be suitable for replication in a unicellular host, such as yeast or bacteria, but may also be intended for introduction to (with and without integration within the genome) cultured mammalian or plant or other eukaryotic cell lines. The purification of nucleic acids produced by the methods of the present invention is described, e.g., in Sambrook et al., 1989 or Ausubel et al., 1992.

The polynucleotides of the present invention may also be produced by chemical synthesis, e.g., by the phosphoramidite method described by Beaucage & Carruthers, 1981 or the triester method according to Matteucci and Caruthers, 1981, and may be performed on commercial, automated oligonucleotide synthesizers. A double-stranded fragment may be obtained from the single-stranded product of chemical synthesis either by synthesizing the complementary strand and annealing the strands together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Polynucleotide constructs prepared for introduction into a prokaryotic or eukaryotic host may comprise a replication system recognized by the host, including the intended polynucleotide fragment encoding the desired polypeptide, and will preferably also include transcription and translational initiation regulatory sequences operably linked to the polypeptide encoding segment. Expression vectors may include, for example, an origin of replication or autonomously replicating sequence (ARS) and expression control sequences, a promoter, an enhancer and necessary processing information sites, such as ribosome-binding sites, RNA splice sites, polyadenylation sites, transcriptional terminator sequences, and mRNA stabilizing sequences. Secretion signals may also be included where appropriate, whether from a native BRCA1 protein or from other receptors or from secreted polypeptides of the same or related species, which allow the protein to cross and/or lodge in cell membranes, and thus attain its functional topology, or be secreted from the cell. Such vectors may be prepared by means of standard recombinant techniques well known in the art and discussed, for example, in Sambrook et al., 1989 or Ausubel et al. 1992.

An appropriate promoter and other necessary vector sequences will be selected so as to be functional in the host, and may include, when appropriate, those naturally associated with BRCA1 genes. Examples of workable combinations of cell lines and expression vectors are described in Sambrook et al., 1989 or Ausubel et al., 1992; see also, e.g., Metzger et al., 1988. Many useful vectors are known in the art and may be obtained from such vendors as Stratagene, New England Biolabs, Promega Biotech, and others. Promoters such as the trp, lac and phage promoters, tRNA promoters and glycolytic enzyme promoters may be used in prokaryotic hosts. Useful yeast promoters include promoter regions for metallothionein, 3-phosphoglycerate kinase or other glycolytic enzymes such as enolase or glyceraldehyde-3-phosphate dehydrogenase, enzymes responsible for maltose and galactose utilization, and others. Vectors and promoters suitable for use in yeast expression are further described in Hitzeman et al., EP 73,675A. Appropriate non-native mammalian promoters might include the early and late promoters from SV40 (Fiers et al., 1978) or promoters derived from murine Moloney leukemia virus, mouse tumor virus, avian sarcoma viruses, adenovirus II, bovine papilloma virus or polyoma. In addition, the construct may be joined to an amplifiable gene (e.g., DHFR) so that multiple copies of the gene may be made. For appropriate enhancer and other expression control sequences, see also Enhancers and Eukaryotic Gene Expression, Cold Spring Harbor Press, Cold Spring Harbor, N. Y. (1983).

While such expression vectors may replicate autonomously, they may also replicate by being inserted into the genome of the host cell, by methods well known in the art.

Expression and cloning vectors will likely contain a selectable marker, a gene encoding a protein necessary for survival or growth of a host cell transformed with the vector. The presence of this gene ensures growth of only those host cells which express the inserts. Typical selection genes encode proteins that a) confer resistance to antibiotics or other toxic substances, e.g. ampicillin, neomycin, methotrexate, etc.; b) complement auxotrophic deficiencies, or c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for Bacilli. The choice of the proper selectable marker will depend on the host cell, and appropriate markers for different hosts are well known in the art.

The vectors containing the nucleic acids of interest can be transcribed in vitro, and the resulting RNA introduced into the host cell by well-known methods, e.g., by injection (see, Kubo et al., 1988), or the vectors can be introduced directly into host cells by methods well known in the art, which vary depending on the type of cellular host, including electroporation; transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; infection (where the vector is an infectious agent, such as a retroviral genome); and other methods. See generally, Sambrook et al., 1989 and Ausubel et al., 1992. The introduction of the polynucleotides into the host cell by any method known in the art, including, inter alia, those described above, will be referred to herein as "transformation." The cells into which have been introduced nucleic acids described above are meant to also include the progeny of such cells.

Large quantities of the nucleic acids and polypeptides of the present invention may be prepared by expressing the BRCA1 nucleic acids or portions thereof in vectors or other expression vehicles in compatible prokaryotic or eukaryotic host cells. The most commonly used prokaryotic hosts are strains of *Escherichia coli*, although other prokaryotes, such as *Bacillus subtilis* or Pseudomonas may also be used.

Mammalian or other eukaryotic host cells, such as those of yeast, filamentous fungi, plant, insect, or amphibian or avian species, may also be useful for production of the proteins of the present invention. Propagation of mammalian cells in culture is per se well known. See, Jakoby and Pastan, 1979. Examples of commonly used mammalian host cell lines are VERO and HeLa cells, Chinese hamster ovary (CHO) cells, and WI38, BHK, and COS cell lines, although it will be appreciated by the skilled practitioner that other cell lines may be appropriate, e.g., to provide higher expression, desirable glycosylation patterns, or other features.

Clones are selected by using markers depending on the mode of the vector construction. The marker may be on the same or a different DNA molecule, preferably the same DNA molecule. In prokaryotic hosts, the transformant may be selected, e.g., by resistance to ampicillin, tetracycline or other antibiotics. Production of a particular product based on temperature sensitivity may also serve as an appropriate marker.

Prokaryotic or eukaryotic cells transformed with the polynucleotides of the present invention will be useful not only for the production of the nucleic acids and polypeptides of the present invention, but also, for example, in studying the characteristics of BRCA1 polypeptides.

Antisense polynucleotide sequences are useful in preventing or diminishing the expression of the BRCA1 locus, as will be appreciated by those skilled in the art. For example, polynucleotide vectors containing all or a portion of the BRCA1 locus or other sequences from the BRCA1 region (particularly those flanking the BRCA1 locus) may be placed under the control of a promoter in an antisense orientation and introduced into a cell. Expression of such an antisense construct within a cell will interfere with BRCA1 transcription and/or translation and/or replication.

The probes and primers based on the BRCA1 gene sequences disclosed herein are used to identify homologous BRCA1 gene sequences and proteins in other species. These BRCA1 gene sequences and proteins are used in the diagnostic/prognostic, therapeutic and drug screening methods described herein for the species from which they have been isolated.

Methods of Use: Nucleic Acid Diagnosis and Diagnostic Kits

In order to detect the presence of a BRCA1 allele predisposing an individual to cancer, a biological sample such as blood is prepared and analyzed for the presence or absence of susceptibility alleles of BRCA1. In order to detect the presence of neoplasia, the progression toward malignancy of a precursor lesion, or as a prognostic indicator, a biological sample of the lesion is prepared and analyzed for the presence or absence of mutant alleles of BRCA1. Results of these tests and interpretive information are returned to the health care provider for communication to the tested individual. Such diagnoses may be performed by diagnostic laboratories, or, alternatively, diagnostic kits are manufactured and sold to health care providers or to private individuals for self-diagnosis.

Initially, the screening method involves amplification of the relevant BRCA1 sequences. In another preferred embodiment of the invention, the screening method involves a non-PCR based strategy. Such screening methods include two-step label amplification methodologies that are well known in the art. Both PCR and non-PCR based screening strategies can detect target sequences with a high level of sensitivity.

The most popular method used today is target amplification. Here, the target nucleic acid sequence is amplified with polymerases. One particularly preferred method using polymerase-driven amplification is the polymerase chain reaction (PCR). The polymerase chain reaction and other polymerase-driven amplification assays can achieve over a million-fold increase in copy number through the use of polymerase-driven amplification cycles. Once amplified, the resulting nucleic acid can be sequenced or used as a substrate for DNA probes.

When the probes are used to detect the presence of the target sequences (for example, in screening for cancer susceptibility), the biological sample to be analyzed, such as blood or serum, may be treated, if desired, to extract the nucleic acids. The sample nucleic acid may be prepared in various ways to facilitate detection of the target sequence; e.g. denaturation, restriction digestion, electrophoresis or dot blotting. The targeted region of the analyte nucleic acid usually must be at least partially single-stranded to form hybrids with the targeting sequence of the probe. If the sequence is naturally single-stranded, denaturation will not be required. However, if the sequence is double-stranded, the sequence will probably need to be denatured. Denaturation can be carried out by various techniques known in the art.

Analyte nucleic acid and probe are incubated under conditions which promote stable hybrid formation of the target sequence in the probe with the putative targeted sequence in the analyte. The region of the probes which is used to bind to the analyte can be made completely complementary to the targeted region of human chromosome 17q. Therefore, high stringency conditions are desirable in order to prevent false positives. However, conditions of high stringency are used only if the probes are complementary to regions of the chromosome which are unique in the genome. The stringency of hybridization is determined by a number of factors during hybridization and during the washing procedure, including temperature, ionic strength, base composition, probe length, and concentration of formamide. These factors are outlined in, for example, Maniatis et al., 1982 and Sambrook et al., 1989. Under certain circumstances, the formation of higher order hybrids, such as triplexes, quadraplexes, etc., may be desired to provide the means of detecting target sequences.

Detection, if any, of the resulting hybrid is usually accomplished by the use of labeled probes. Alternatively, the probe may be unlabeled, but may be detectable by specific binding with a ligand which is labeled, either directly or indirectly. Suitable labels, and methods for labeling probes and ligands are known in the art, and include, for example, radioactive labels which may be incorporated by known methods (e.g., nick translation, random priming or kinasing), biotin, fluorescent groups, chemiluminescent groups (e.g., dioxetanes, particularly triggered dioxetanes), enzymes, antibodies and the like. Variations of this basic scheme are known in the art, and include those variations that facilitate separation of the hybrids to be detected from extraneous materials and/or that amplify the signal from the labeled moiety. A number of these variations are reviewed in, e.g., Matthews & Kricka, 1988; Landegren et al., 1988; Mittlin, 1989; U.S. Pat. No. 4,868,105, and in EPO Publication No. 225,807.

As noted above, non-PCR based screening assays are also contemplated in this invention. An exemplary non-PCR based procedure is provided in Example 11. This procedure hybridizes a nucleic acid probe (or an analog such as a methyl phosphonate backbone replacing the normal phosphodiester), to the low level DNA target. This probe may have an enzyme covalently linked to the probe, such that the covalent linkage does not interfere with the specificity of the hybridization. This enzyme-probe-conjugate-target nucleic acid complex can then be isolated away from the free probe enzyme conjugate and a substrate is added for enzyme detection. Enzymatic activity is observed as a change in color development or luminescent output resulting in a 10^3–10^6 increase in sensitivity. For an example relating to the preparation of oligodeoxynucleotide-alkaline phosphatase conjugates and their use as hybridization probes see Jablonski et al., 1986.

Two-step label amplification methodologies are known in the art. These assays work on the principle that a small ligand (such as digoxigenin, biotin, or the like) is attached to a nucleic acid probe capable of specifically binding BRCA1. Exemplary probes are provided in Table 9 of this patent application and additionally include the nucleic acid probe corresponding to nucleotide positions 3631 to 3930 of SEQ ID NO:1. Allele specific probes are also contemplated within the scope of this example and exemplary allele specific probes include probes encompassing the predisposing mutations summarized in Tables 11 and 12 of this patent application.

In one example, the small ligand attached to the nucleic acid probe is specifically recognized by an antibody-enzyme conjugate. In one embodiment of this example, digoxigenin is attached to the nucleic acid probe. Hybridization is detected by an antibody-alkaline phosphatase conjugate which turns over a chemiluminescent substrate. For methods for labeling nucleic acid probes according to this embodiment see Martin et al., 1990. In a second example, the small ligand is recognized by a second ligand-enzyme conjugate that is capable of specifically complexing to the first ligand. A well known embodiment of this example is the biotin-avidin type of interactions. For methods for labeling nucleic acid probes and their use in biotin-avidin based assays see Rigby et al., 1977 and Nguyen et al., 1992.

It is also contemplated within the scope of this invention that the nucleic acid probe assays of this invention will employ a cocktail of nucleic acid probes capable of detecting BRCA1. Thus, in one example to detect the presence of BRCA1 in a cell sample, more than one probe complementary to BRCA1 is employed and in particular the number of different probes is alternatively 2, 3, or 5 different nucleic acid probe sequences. In another example, to detect the presence of mutations in the BRCA1 gene sequence in a patient, more than one probe complementary to BRCA1 is employed where the cocktail includes probes capable of binding to the allele-specific mutations identified in populations of patients with alterations in BRCA1. In this embodiment, any number of probes can be used, and will preferably include probes corresponding to the major gene mutations identified as predisposing an individual to breast cancer. Some candidate probes contemplated within the scope of the invention include probes that include the allele-specific mutations identified in Tables 11 and 12 and those that have the BRCA1 regions corresponding to SEQ ID NO:1 both 5' and 3' to the mutation site.

Methods of Use: Peptide Diagnosis and Diagnostic Kits

The neoplastic condition of lesions can also be detected on the basis of the alteration of wild-type BRCA1 polypeptide. Such alterations can be determined by sequence analysis in accordance with conventional techniques. More preferably, antibodies (polyclonal or monoclonal) are used to detect differences in, or the absence of BRCA1 peptides. The antibodies may be prepared as discussed above under the heading "Antibodies" and as further shown in Examples 12 and 13. Other techniques for raising and purifying antibodies are well known in the art and any such techniques may be chosen to achieve the preparations claimed in this invention. In a preferred embodiment of the invention, antibodies will immunoprecipitate BRCA1 proteins from solution as well as react with BRCA1 protein on Western or immunoblots of polyacrylamide gels. In another preferred embodiment, antibodies will detect BRCA1 proteins in paraffin or frozen tissue sections, using immunocytochemical techniques.

Preferred embodiments relating to methods for detecting BRCA1 or its mutations include enzyme linked immunosorbent assays (ELISA), radioimmunoassays (RIA), immunoradiometric assays (IRMA) and immtunloenzymatic assays (IEMA), including sandwich assays using monoclonal and/or polyclonal antibodies. Exemplary sandwich assays are described by David et al. in U.S. Pat. Nos. 5 4,376,110 and 4,486,530, hereby incorporated by reference, and exemplified in Example 14.

Methods of Use: Drug Screening

This invention is particularly useful for screening compounds by using the BRCA1 polypeptide or binding fragment thereof in any of a variety of drug screening techniques.

The BRCA1 polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, or borne on a cell surface. One method of drug screening utilizes eucaryotic or procaryotic host cells which are stably transformed with recombinant polynucleotides expressing the polypeptide or fragment, preferably in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, for the formation of complexes between a BRCA1 polypeptide or fragment and the agent being tested, or examine the degree to which the formation of a complex between a BRCA1 polypeptide or fragment and a known ligand is interfered with by the agent being tested.

Thus, the present invention provides methods of screening for drugs comprising contacting such an agent with a BRCA1 polypeptide or fragment thereof and assaying (i) for the presence of a complex between the agent and the BRCA1 polypeptide or fragment, or (ii) for the presence of a complex between the BRCA1 polypeptide or fragment and a ligand, by methods well known in the art. In such competitive binding assays the BRCA1 polypeptide or fragment is typically labeled. Free BRCA1 polypeptide or fragment is separated from that present in a protein:protein complex, and the amount of free (i.e., uncomplexed) label is a measure of the binding of the agent being tested to BRCA1 or its interference with BRCA1:ligand binding, respectively.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the BRCA1 polypeptides and is described in detail in Geysen, PCT published application WO 84/03564, published on Sep. 13, 1984. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with BRCA1 polypeptide and washed. Bound BRCA1 polypeptide is then detected by methods well known in the art.

Purified BRCA1 can be coated directly onto plates for use in the aforementioned drug screening techniques. However, non-neutralizing antibodies to the polypeptide can be used to capture antibodies to immobilize the BRCA1 polypeptide on the solid phase.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of specifically binding the BRCA1 polypeptide compete with a test compound for binding to the BRCA1 polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants of the BRCA1 polypeptide.

A further technique for drug screening involves the use of host eukaryotic cell lines or cells (such as described above) which have a nonfunctional BRCA1 gene. These host cell lines or cells are defective at the BRCA1 polypeptide level. The host cell lines or cells are grown in the presence of drug compound. The rate of growth of the host cells is measured to determine if the compound is capable of regulating the growth of BRCA1 defective cells.

Methods of Use: Rational Drug Design

The goal of rational drug design is to produce structural analogs of biologically active polypeptides of interest or of small molecules with which they interact (e.g., agonists, antagonists, inhibitors) in order to fashion drugs which are, for example, more active or stable forms of the polypeptide, or which, e.g., enhance or interfere with the function of a polypeptide in vivo. See, e.g., Hodgson, 1991. In one approach, one first determines the three-dimensional structure of a protein of interest (e.g., BRCA1 polypeptide) or, for example, of the BRCA1-receptor or ligand complex, by x-ray crystallography, by computer modeling or most typically, by a combination of approaches. Less often, useful information regarding the structure of a polypeptide may be gained by modeling based on the structure of homologous proteins. An example of rational drug design is the development of HIV protease inhibitors (Erickson et al., 1990). In addition, peptides (e.g., BRCA1 polypeptide) are analyzed by an alanine scan (Wells, 1991). In this technique, an amino acid residue is replaced by Ala, and its effect on the peptide's activity is determined. Each of the amino acid residues of the peptide is analyzed in this manner to determine the important regions of the peptide.

It is also possible to isolate a target-specific antibody, selected by a functional assay, and then to solve its crystal structure. In principle, this approach yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idio-typic antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced banks of peptides. Selected peptides would then act as the pharmacore.

Thus, one may design drugs which have, e.g., improved BRCA1 polypeptide activity or stability or which act as inhibitors, agonists, antagonists, etc. of BRCA1 polypeptide activity. By virtue of the availability of cloned BRCA1 sequences, sufficient amounts of the BRCA1 polypeptide may be made available to perform such analytical studies as x-ray crystallography. In addition, the knowledge of the BRCA1 protein sequence provided herein will guide those employing computer modeling techniques in place of, or in addition to x-ray crystallography.

Methods of Use: Gene Therapy

According to the present invention, a method is also provided of supplying wild-type BRCA1 function to a cell which carries mutant BRCA1 alleles. Supplying such a function should suppress neoplastic growth of the recipient cells. The wild-type BRCA1 gene or a part of the gene may be introduced into the cell in a vector such that the gene remains extrachromosomal. In such a situation, the gene will be expressed by the cell from the extrachromosomal location. If a gene fragment is introduced and expressed in a cell carrying a mutant BRCA1 allele, the gene fragment should encode a part of the BRCA1 protein which is required for non-neoplastic growth of the cell. More preferred is the situation where the wild-type BRCA1 gene or a part thereof is introduced into the mutant cell in such a way that it recombines with the endogenous mutant BRCA1 gene present in the cell. Such recombination requires a double recombination event which results in the correction of the BRCA1 gene mutation. Vectors for introduction of genes both for recombination and for extrachromosomal maintenance are known in the art, and any suitable vector may be used. Methods for introducing DNA into cells such as electroporation, calcium phosphate co-precipitation and viral transduction are known in the art, and the choice of method is within the competence of the routineer. Cells transformed with the wild-type BRCA1 gene can be used as model systems to study cancer remission and drug treatments which promote such remission.

As generally discussed above, the BRCA1 gene or fragment, where applicable, may be employed in gene therapy methods in order to increase the amount of the expression products of such genes in cancer cells. Such gene therapy is particularly appropriate for use in both cancerous and pre-cancerous cells, in which the level of BRCA1 polypeptide is absent or diminished compared to normal cells. It may also be useful to increase the level of expression of a given BRCA1 gene even in those tumor cells in which the mutant gene is expressed at a "normal" level, but the gene product is not fully functional.

Gene therapy would be carried out according to generally accepted methods, for example, as described by Friedman, 1991. Cells from a patient's tumor would be first analyzed by the diagnostic methods described above, to ascertain the production of BRCA1 polypeptide in the tumor cells. A virus or plasmid vector (see further details below), containing a copy of the BRCA1 gene linked to expression control elements and capable of replicating inside the tumor cells, is prepared. Suitable vectors are known, such as disclosed in U.S. Pat. No. 5,252,479 and PCT published application WO 93/07282. The vector is then injected into the patient, either locally at the site of the tumor or systemically (in order to reach any tumor cells that may have metastasized to other sites). If the transfected gene is not permanently incorporated into the genome of each of the targeted tumor cells, the treatment may have to be repeated periodically.

Gene transfer systems known in the art may be useful in the practice of the gene therapy methods of the present invention. These include viral and nonviral transfer methods. A number of viruses have been used as gene transfer vectors, including papovaviruses, e.g., SV40 (Madzak et al., 1992), adenovirus (Berkner, 1992; Berkner et al., 1988; Gorziglia and Kapikian, 1992; Quantin et al., 1992; Rosenfeld et al., 1992; Wilkinson et al., 1992; Stratford-Perricaudet et al., 1990), vaccinia virus (Moss, 1992), adenomatus-associated virus (Muzyczka, 1992; Ohi et al., 1990), herpesviruses including HSV and EBV (Margolskee, 1992; Johnson et al., 1992; Fink et al., 1992; Breakfield and Geller, 1987; Freese et al., 1990), and retroviruses of avian (Brandyopadhyay and Temin, 1984; Petropoulos et al., 1992), murine (Miller, 1992; Miller et al., 1985; Sorge et al., 1984; Mann and Baltimore, 1985; Miller et al., 1988), and human origin (Shimada et al., 1991; Helseth et al., 1990; Page et al., 1990; Buchschacher and Panganiban, 1992). Most human gene therapy protocols have been based on disabled murine retroviruses.

Nonviral gene transfer methods known in the art include chemical techniques such as calcium phosphate coprecipitation (Graham and van der Eb, 1973; Pellicer et al., 1980); mechanical techniques, for example microinjection (Anderson et al., 1980; Gordon et al., 1980; Brinster et al., 1981; Constantini and Lacy, 1981); membrane fusion-mediated transfer via liposomes (Felgner et al., 1987; Wang and Huang, 1989; Kaneda et al., 1989; Stewart et al., 1992; Nabel et al., 1990; Lim et al., 1992); and direct DNA uptake and receptor-mediated DNA transfer (Wolff et al., 1990; Wu et al., 1991; Zenke et al., 1990; Wu et al., 1989b; Wolff et al., 1991; Wagner et al., 1990; Wagner et al., 1991; Cotten et al., 1990; Curiel et al., 1991a; Curiel et al., 1991b). Viral-mediated gene transfer can be combined with direct in vivo gene transfer using liposome delivery, allowing one to direct the viral vectors to the tumor cells and not into the surrounding nondividing cells. Alternatively, the retroviral vector producer cell line can be injected into tumors (Culver et al., 1992). Injection of producer cells would then provide a continuous source of vector particles. This technique has been approved for use in humans with inoperable brain tumors.

In an approach which combines biological and physical gene transfer methods, plasmid DNA of any size is combined with a polylysine-conjugated antibody specific to the adenovirus hexon protein, and the resulting complex is bound to an adenovirus vector. The trimolecular complex is then used to infect cells. The adenovirus vector permits efficient binding, internalization, and degradation of the endosome before the coupled DNA is damaged.

Liposome/DNA complexes have been shown to be capable of mediating direct in vivo gene transfer. While in standard liposome preparations the gene transfer process is nonspecific, localized in vivo uptake and expression have been reported in tumor deposits, for example, following direct in situ administration (Nabel, 1992).

Gene transfer techniques which target DNA directly to breast and ovarian tissues, e.g., epithelial cells of the breast or ovaries, is preferred. Receptor-mediated gene transfer, for example, is accomplished by the conjugation of DNA (usually in the form of covalently closed supercoiled plasmid) to a protein ligand via polylysine. Ligands are chosen on the basis of the presence of the corresponding ligand receptors on the cell surface of the target cell/tissue type. One appropriate receptor/ligand pair may include the estrogen receptor and its ligand, estrogen (and estrogen analogues). These ligand-DNA conjugates can be injected directly into the blood if desired and are directed to the target tissue where receptor binding and internalization of the DNA-protein complex occurs. To overcome the problem of intracellular destruction of DNA, coinfection with adenovirus can be included to disrupt endosome function.

The therapy involves two steps which can be performed singly or jointly. In the first step, prepubescent females who carry a BRCA1 susceptibility allele are treated with a gene delivery vehicle such that some or all of their mammary ductal epithelial precursor cells receive at least one additional copy of a functional normal BRCA1 allele. In this step, the treated individuals have reduced risk of breast cancer to the extent that the effect of the susceptible allele has been countered by the presence of the normal allele. In the second step of a preventive therapy, predisposed young females, in particular women who have received the proposed gene therapeutic treatment, undergo hormonal therapy to mimic the effects on the breast of a full term pregnancy.

Methods of Use: Peptide Therapy

Peptides which have BRCA1 activity can be supplied to cells which carry mutant or missing BRCA1 alleles. The sequence of the BRCA1 protein is disclosed (SEQ ID NO:2). Protein can be produced by expression of the cDNA sequence in bacteria, for example, using known expression vectors. Alternatively, BRCA1 polypeptide can be extracted from BRCA1-producing mammalian cells. In addition, the techniques of synthetic chemistry can be employed to synthesize BRCA1 protein. Any of such techniques can provide the preparation of the present invention which comprises the BRCA1 protein. The preparation is substantially free of other human proteins. This is most readily accomplished by synthesis in a microorganism or in vitro.

Active BRCA1 molecules can be introduced into cells by microinjection or by use of liposomes, for example. Alternatively, some active molecules may be taken up by cells, actively or by diffusion. Extracellular application of the BRCA1 gene product may be sufficient to affect tumor growth. Supply of molecules with BRCA1 activity should lead to partial reversal of the neoplastic state. Other molecules with BRCA1 activity (for example, peptides, drugs or organic compounds) may also be used to effect such a reversal. Modified polypeptides having substantially similar function are also used for peptide therapy.

Methods of Use: Transformed Hosts

Similarly, cells and animals which carry a mutant BRCA1 allele can be used as model systems to study and test for substances which have potential as therapeutic agents. The cells are typically cultured epithelial cells. These may be isolated from individuals with BRCA1 mutations, either somatic or germline. Alternatively, the cell line can be engineered to carry the mutation in the BRCA1 allele, as described above. After a test substance is applied to the cells, the neoplastically transformed phenotype of the cell is determined. Any trait of neoplastically transformed cells can be assessed, including anchorage-independent growth, tumorigenicity in nude mice, invasiveness of cells, and growth factor dependence. Assays for each of these traits are known in the art.

Animals for testing therapeutic agents can be selected after mutagenesis of whole animals or after treatment of germline cells or zygotes. Such treatments include insertion of mutant BRCA1 alleles, usually from a second animal species, as well as insertion of disrupted homologous genes. Alternatively, the endogenous BRCA1 gene(s) of the animals may be disrupted by insertion or deletion mutation or other genetic alterations using conventional techniques (Capecchi, 1989; Valancius and Smithies, 1991; Hasty et al., 1991; Shinkai et al., 1992; Mombaerts et al., 1992; Philpott et al., 1992; Snouwaert et al., 1992; Donehower et al., 1992). After test substances have been administered to the animals, the growth of tumors must be assessed. If the test substance prevents or suppresses the growth of tumors, then the test substance is a candidate therapeutic agent for the treatment of the cancers identified herein. These animal models provide an extremely important testing vehicle for potential therapeutic products.

The present invention is described by reference to the following Examples, which are offered by way of illustration and are not intended to limit the invention in any manner. Standard techniques well known in the art or the techniques specifically described below were utilized.

EXAMPLE 1

Ascertain and Study Kindreds Likely to Have a 17q-Linked Breast Cancer Susceptibility Locus

Extensive cancer prone kindreds were ascertained by our University of Utah collaborators from a defined population providing a large set of extended kindreds with multiple cases of breast cancer and many relatives available to study. The large number of meioses present in these large kindreds provided the power to detect whether the BRCA1 locus was segregating, and increased the opportunity for informative recombinants to occur within the small region being investigated. This vastly improved the chances of establishing linkage to the BRCA1 region, and greatly facilitated the reduction of the BRCA1 region to a manageable size, which permits identification of the BRCA1 locus itself.

Each kindred was extended through all available connecting relatives by our collaborators, and to all informative first degree relatives of each proband or cancer case. For these kindreds, additional breast cancer cases and individuals with cancer at other sites of interest (e.g. ovarian) who also appeared in the kindreds were identified through the tumor registry linked files. All breast cancers reported in the kindred which were not confirmed in the Utah Cancer Registry were researched. Medical records or death certificates were obtained for confirmation of all cancers. Each key connecting individual and all informative individuals were invited by our collaborators to participate by providing a blood sample from which DNA was extracted. They also sampled spouses and relatives of deceased cases so that the genotype of the deceased cases could be inferred from the genotypes of their relatives.

Ten kindreds which had three or more cancer cases with inferable genotypes were selected for linkage studies to 17q markers from a set of 29 kindreds originally ascertained for a study of proliferative breast disease and breast cancer (Skolnick et al., 1990). The criterion for selection of these kindreds was the presence of two sisters or a mother and her daughter with breast cancer. Additionally, two kindreds which have been studied by our collaborators since 1980 as part of their breast cancer linkage studies (K1001, K9018), six kindreds ascertained for the presence of clusters of breast and/or ovarian cancer (K2019, K2073, K2079, K2080, K2039, K2082) and a self-referred kindred with early onset breast cancer (K2035) were included. These kindreds were investigated and expanded in our collaborators clinic in the manner described above. Table 1 displays the characteristics of these 19 kindreds which are the subject of subsequent examples. In Table 1, for each kindred the total number of individuals in our database, the number of typed individuals, and the minimum, median, and maximum age at diagnosis of breast/ovarian cancer are reported. Kindreds are sorted in ascending order of median age at diagnosis of breast cancer. Four women diagnosed with both ovarian and breast cancer are counted in both categories.

TABLE 1

Description of the 19 Kindreds

	No. of Individuals		Breast				Ovarian			
				Age at Dx				Age at Dx		
KINDRED	Total	Sample	# Aff.	Min.	Med.	Max.	# Aff.	Min	Med.	Max.
1910	15	10	4	27	34	49	—	—	—	—
1001	133	98	13	28	37	64	—	—	—	—
2035	42	25	8	28	37	45	1	—	60	—
2027	21	11	4	34	38	41	—	—	—	—
9018	54	17	9	30	40	72	2	46	48	50
1925	50	27	4	39	42	53	—	—	—	—
1927	49	29	5	32	42	51	—	—	—	—
1911	28	21	7	28	42	76	—	—	—	—
1929	16	11	4	34	43	73	—	—	—	—
1901	35	19	10	31	44	76	—	—	—	—
2082	180	105	20	27	47	67	10	45	52	66
2019	42	19	10	42	53	79	—	—	—	—
1900	70	23	8	45	55	70	1	—	78	—

TABLE 1-continued

Description of the 19 Kindreds

	No. of Individuals		Breast				Ovarian			
				Age at Dx				Age at Dx		
KINDRED	Total	Sample	# Aff.	Min.	Med.	Max.	# Aff.	Min.	Med.	Max.
2080	264	74	22+	27	55	92	4	45	53	71
2073	57	29	9	35	57	80	—	—	—	—
1917	16	6	4	43	58	61	—	—	—	—
1920	22	14	3	62	63	68	—	—	—	—
2079	136	18	14	38	66	84	4	52	59	65
2039	87	40	14	44	68	88	4	41	51	75

+Includes one case of male breast cancer.

EXAMPLE 2

Selection of Kindreds Which are Linked to Chromosome 17q and Localization of BRCA1 to the Interval Mfd15–Mfd188

For each sample collected in these 19 kindreds, DNA was extracted from blood (or in two cases from paraffin-embedded tissue blocks) using standard laboratory protocols. Genotyping in this study was restricted to short tandem repeat (STR) markers since, in general, they have high heterozygosity and PCR methods offer rapid turnaround while using very small amounts of DNA. To aid in this effort, four such STR markers on chromosome 17 were developed by screening a chromosome specific cosmid library for CA positive clones. Three of these markers localized to the long arm: (46E6, Easton et al., 1993); (42D6, Easton et al., 1993); 26C2 (D17S514, Oliphant et al., 1991), while the other, 12G6 (D17S513, Oliphant et al., 1991), localized to the short arm near the p53 tumor suppressor locus. Two of these, 42D6 and 46E6, were submitted to the Breast Cancer Linkage Consortium for typing of breast cancer families by investigators worldwide. Oligonucleotide sequences for markers not developed in our laboratory were obtained from published reports, or as part of the Breast Cancer Linkage Consortium, or from other investigators. All genotyping films were scored blindly with a standard lane marker used to maintain consistent coding of alleles. Key samples in the four kindreds presented here underwent duplicate typing for all relevant markers. All 19 kindreds have been typed for two polymorphic CA repeat markers: 42D6 (D17S588), a CA repeat isolated in our laboratory, and Mfd15 (D17S250), a CA repeat provided by J. Weber (Weber et al., 1990). Several sources of probes were used to create genetic markers on chromosome 17, specifically chromosome 17 cosmid and lambda phage libraries created from sorted chromosomes by the Los Alamos National Laboratories (van Dilla et al., 1986).

LOD scores for each kindred with these two markers (42D6, Mfd15) and a third marker, Mfd188 (D17S579, Hall et al., 1992), located roughly midway between these two markers, were calculated for two values of the recombination fraction, 0.001 and 0.1. (For calculation of LOD scores, see Oh, 1985). Likelihoods were computed under the model derived by Claus et al., 1991, which assumes an estimated gene frequency of 0.003, a lifetime risk in gene carriers of about 0.80, and population based age-specific risks for breast cancer in non-gene carriers. Allele frequencies for the three markers used for the LOD score calculations were calculated from our own laboratory typings of unrelated individuals in the CEPH panel (White and Lalouel, 1988).

Table 2 shows the results of the pairwise linkage analysis of each kindred with the three markers 42D6, Mfd188, and Mfd15.

TABLE 2

Pairwise Linkage Analysis of Kindreds

	Mfd15 (D17S250) Recombination		Mfd188 (D17S579) Recombination		42D6 (D17S588) Recombination	
KINDRED	0.001	0.1	0.001	0.1	0.001	0.1
1910	0.06	0.30	0.06	0.30	0.06	0.30
1001	−0.30	−0.09	NT	NT	−0.52	−0.19
2035	2.34	1.85	0.94	0.90	2.34	1.82
2027	−1.22	−0.33	−1.20	−0.42	−1.16	−0.33
9018	−0.54	−0.22	−0.17	−0.10	0.11	0.07
1925	1.08	0.79	0.55	0.38	−0.11	−0.07
1927	−0.41	0.01	−0.35	0.07	−0.44	−0.02
1911	−0.27	−0.13	−0.43	−0.23	0.49	0.38
1929	−0.49	−0.25	NT	NT	−0.49	−0.25
1901	1.50	1.17	0.78	0.57	0.65	0.37
2082	4.25	3.36	6.07	5.11	2.00	3.56
2019	−0.10	−0.01	−0.11	−0.05	−0.18	−0.10
1900	−0.14	−0.11	NT	NT	−0.12	−0.05
2080	−0.16	−0.04	0.76	0.74	−1.25	−0.58
2073	−0.41	−0.29	0.63	0.49	−0.23	−0.13
1917	−0.02	−0.02	NT	NT	−0.01	0.00
1920	−0.03	−0.02	NT	NT	0.00	0.00
2079	0.02	0.01	−0.01	−0.01	0.01	0.01
2039	−1.67	−0.83	0.12	0.59	−1.15	0.02

NT—Kindred not typed for mfd188.

Using a criterion for linkage to 17q of a LOD score>1.0 for at least one locus under the CASH model (Claus et al., 1991), four of the 19 kindreds appeared to be linked to 17q (K1901, K1925, K2035, K2082). A number of additional kindreds showed some evidence of linkage but at this time could not be definitively assigned to the linked category. These included kindreds K1911, K2073, K2039, and K2080. Three of the 17q-linked kindreds had informative recombinants in this region and these are detailed below.

Kindred 2082 is the largest 17q-linked breast cancer family reported to date by any group. The kindred contains 20 cases of breast cancer, and ten cases of ovarian cancer. Two cases have both ovarian and breast cancer. The evidence of linkage to 17q for this family is overwhelming; the LOD score with the linked haplotype is over 6.0, despite the existence of three cases of breast cancer which appear to be sporadic, i.e., these cases share no part of the linked haplotype between Mfd15 and 42D6. These three sporadic cases were diagnosed with breast cancer at ages 46, 47, and 54. In smaller kindreds, sporadic cancers of this type greatly confound the analysis of linkage and the correct identification of key recombinants. The key recombinant in the 2082 kindred is a woman who developed ovarian cancer at age 45 whose mother and aunt had ovarian cancer at ages 58 and 66, respectively. She inherited the linked portion of the haplotype for both Mfd188 and 42D6 while inheriting unlinked alleles at Mfd15; this recombinant event placed BRCA1 distal to Mfd15.

K1901 is typical of early-onset breast cancer kindreds. The kindred contains 10 cases of breast cancer with a median age at diagnosis of 43.5 years of age; four cases were diagnosed under age 40. The LOD score for this kindred with the marker 42D6 is 1.5, resulting in a posterior probability of 17q-linkage of 0.96. Examination of haplotypes in this kindred identified a recombinant haplotype in an obligate male carrier and his affected daughter who was diagnosed with breast cancer at age 45. Their linked allele for marker Mfd15 differs from that found in all other cases in the kindred (except one case which could not be completely inferred from her children). The two haplotypes are identical for Mfd188 and 42D6. Accordingly, data from Kindred 1901 would also place the BRCA1 locus distal to Mfd15.

Kindred 2035 is similar to K1901 in disease phenotype. The median age of diagnosis for the eight cases of breast cancer in this kindred is 37. One case also had ovarian cancer at age 60. The breast cancer cases in this family descend from two sisters who were both unaffected with breast cancer until their death in the eighth decade. Each branch contains four cases of breast cancer with at least one case in each branch having markedly early onset. This kindred has a LOD score of 2.34 with Mfd5. The haplotypes segregating with breast cancer in the two branches share an identical allele at Mfd15 but differ for the distal loci Mfd188 and NM23 (a marker typed as part of the consortium which is located just distal to 42D6 (Hall et al., 1992)). Although the two haplotypes are concordant for marker 42D6, it is likely that the alleles are shared identical by state (the same allele but derived from different ancestors), rather than identical by descent (derived from a common ancestor) since the shared allele is the second most common allele observed at this locus. By contrast the linked allele shared at Mfd15 has a frequency of 0.04. This is a key recombinant in our dataset as it is the sole recombinant in which BRCA1 segregated with the proximal portion of the haplotype, thus setting the distal boundary to the BRCA1 region. For this event not to be a key recombinant requires that a second mutant BRCA1 gene be present in a spouse marrying into the kindred who also shares the rare Mfd15 allele segregating with breast cancer in both branches of the kindred. This event has a probability of less than one in a thousand. The evidence from this kindred therefore placed the BRCA1 locus proximal to Mfd188.

EXAMPLE 3

Creation of a Fine Structure Map and Refinement of the BRCA1 Region to Mfd191-Mfd188 using Additional STR Polymorphisms

In order to improve the characterization of our recombinants and define closer flanking markers, a dense map of this relatively small region on chromosome 17q was required. The chromosome 17 workshop has produced a consensus map of this region (FIG. 1) based on a combination of genetic and physical mapping studies (Fain, 1992). This map contains both highly polymorphic STR polymorphisms, and a number of nonpolymorphic expressed genes. Because this map did not give details on the evidence for this order nor give any measure of local support for inversions in the order of adjacent loci, we viewed it as a rough guide for obtaining resources to be used for the development of new markers and construction of our own detailed genetic and physical map of a small region containing BRCA1. Our approach was to analyze existing STR markers provided by other investigators and any newly developed markers from our laboratory with respect to both a panel of meiotic (genetic) breakpoints identified using DNA from the CEPH reference families and a panel of somatic cell hybrids (physical breakpoints) constructed for this region. These markers included 26C2 developed in our laboratory which maps proximal to Mfd15, Mfd191 (provided by James Weber), THRA1 (Futreal et al., 1992a), and three polymorphisms kindly provided to us by Dr. Donald Black, NM23 (Hall et al. 1992), SCG40 (D17S181), and 6C1 (D17S293).

Genetic localization of markers. In order to localize new markers genetically within the region of interest, we have identified a number of key meiotic breakpoints within the region, both in the CEPH reference panel and in our large breast cancer kindred (K2082). Given the small genetic distance in this region, they are likely to be only a relatively small set of recombinants which can be used for this purpose, and they are likely to group markers into sets. The orders of the markers within each set can only be determined by physical mapping. However the number of genotypings necessary to position a new marker is minimized. These breakpoints are illustrated in Tables 3 and 4. Using this approach we were able to genetically order the markers THRA1, 6C1, SCG40, and Mfd191. As can be seen from Tables 3 and 4, THRA1 and MFD191 both map inside the Mfd15-Mfd188 region we had previously identified as containing the BRCA1 locus. In Tables 3 and 4, M/P indicates a maternal or paternal recombinant. A "1" indicates inherited allele is of grandpaternal origin, while a "0" indicates grandmaternal origin, and "-" indicates that the locus was untyped or uninformative.

TABLE 3

			CEPH Recombinants						
Family	ID	M/P	Mfd15	THRA1	Mfd191	Mfd188	SCG40	6C1	42D6
13292	4	M	1	1	1	0	0	0	0
13294	4	M	1	1	1	0	0	0	0
13294	6	M	0	0	1	1	—	—	—
1334	3	M	1	1	1	1	1	0	0
1333	4	M	1	1	1	0	—	—	0
1333	6	M	0	0	1	1	—	—	1
1333	8	P	1	0	0	0	—	—	0
1377	8	M	0	—	0	0	0	0	1

TABLE 4

Kindred 2082 Recombinants

Family	ID	M/P	Mfd15	Mfd191	Mfd188	SCG40	6C1	42D6
75		M	0	1	1	1	—	—
63		M	0	0	1	1	—	1
125		M	1	1	1	0	—	0
40		M	1	1	0	0	—	0

Analysis of markers Mfd15, Mfd188, Mfd191, and THRA1 in our recombinant families. Mfd15, Mfd188, Mfd191 and THRA1 were typed in our recombinant families and examined for additional information to localize the BRCA1 locus. In kindred 1901, the Mfd15 recombinant was recombinant for THRA1 but uninformative for Mfd191, thus placing BRCA1 distal to THRA1. In K2082, the recombinant with Mfd15 also was recombinant with Mfd191, thus placing the BRCA1 locus distal to Mfd191 (Goldgar et al., 1994). Examination of THRA1 and Mfd191 in kindred K2035 yielded no further localization information as the two branches were concordant for both markers. However, SCG40 and 6C1 both displayed the same pattern as Mfd188, thus increasing our confidence in the localization information provided by the Mfd188 recombinant in this family. The BRCA1 locus, or at least a portion of it, therefore lies within an interval bounded by Mfd191 on the proximal side and Mfd188 on the distal side.

EXAMPLE 4

Development of Genetic and Physical Resources in the Region of Interest

To increase the number of highly polymorphic loci in the Mfd191-Mfd188 region, we developed a number of STR markers in our laboratory from cosmids and YACs which physically map to the region. These markers allowed us to further refine the region.

STSs were identified from genes known to be in the desired region to identify YACs which contained these loci, which were then used to identify subclones in cosmids, P1s or BACs. These subclones were then screened for the presence of a CA tandem repeat using a $(CA)_n$ oligonucleotide (Pharmacia). Clones with a strong signal were selected preferentially, since they were more likely to represent CA-repeats which have a large number of repeats and/or are of near-perfect fidelity to the $(CA)_n$ pattern. Both of these characteristics are known to increase the probability of polymorphism (Weber, 1990). These clones were sequenced directly from the vector to locate the repeat. We obtained a unique sequence on one side of the CA-repeat by using one of a set of possible primers complementary to the end of a CA-repeat, such as $(GT)_{10}T$. Based on this unique sequence, a primer was made to sequence back across the repeat in the other direction, yielding a unique sequence for design of a second primer flanking the CA-repeat. STRs were then screened for polymorphism on a small group of unrelated individuals and tested against the hybrid panel to confirm their physical localization. New markers which satisfied these criteria were then typed in a set of 40 unrelated individuals from the Utah and CEPH families to obtain allele frequencies appropriate for the study population. Many of the other markers reported in this study were tested in a smaller group of CEPH unrelated individuals to obtain similarly appropriate allele frequencies.

Using the procedure described above, a total of eight polymorphic STRs was found from these YACS. Of the loci identified in this manner, four were both polymorphic and localized to the BRCA1 region. Four markers did not localize to chromosome 17, reflecting the chimeric nature of the YACs used. The four markers which were in the region were denoted AA1, ED2, 4–7, and YM29. AA1 and ED2 were developed from YACs positive for the RNU2 gene, 4–7 from an EPB3 YAC and YM29 from a cosmid which localized to the region by the hybrid panel. A description of the number of alleles, heterozygosity and source of these four and all other STR polymorphisms analyzed in the breast cancer kindreds is given below in Table 5.

TABLE 5

Polymorphic Short Tandem Repeat Markers Used for Fine Structure Mapping of the BRCA1 Locus

				Allele* Frequency (%)					
Clone	Gene	Na**	Heterozygosity	1	2	3	4	5	6
Mfd15	D17S250	10	0.82	26	22	15	7	7	23
THRA1	THRA1	5							
Mfd191	D17S776	7	0.55	48	20	11	7	7	7
ED2	D17S1327	12	0.55	62	9	8	5	5	11
AA1	D17S1326	7	0.83	28	28	25	8	6	5
CA375	D17S184	10	0.75	26	15	11	9	9	20
4–7	D17S1183	9	0.50	63	15	8	6	4	4
YM29	—	9	0.62	42	24	12	7	7	8
Mfd188	D17S579	12	0.92	33	18	8	8	8	25
SCG40	D17S181	14	0.90	20	18	18	10	8	35
42D6	D17S588	11	0.86	21	17	11	10	9	32
6C1	D17S293	7	0.75	30	30	11	11	9	9
Z109	D17S750	9	0.70	33	27	7	7	7	19
tdj1475	D17S1321	13	0.84	21	16	11	11	8	33
CF4	D17S1320	6	0.63	50	27	9	7	4	3
tdj1239	D17S1328	10	0.80	56	10	9	7	4	14
U5	D17S1325	13	0.83	19	16	12	10	9	34

*Allele codes 1–5 are listed in decreasing frequency; allele numbers do not correspond to fragment sizes. Allele 6 frequency is the joint frequency of all other alleles for each locus.

**Number of alleles seen in the genetically independent DNA samples used for calculating allele frequencies.

The four STR polymorphisms which mapped physically to the region (4–7, ED2, AA1, YM29) were analyzed in the meiotic, breakpoint panel shown initially in Tables 3 and 4. Tables 6 and 7 contain the relevant CEPH data and Kindred 2082 data for localization of these four markers. In the tables, M/P indicates a maternal or paternal recombinant. A "1" indicates inherited allele is of grandpaternal origin, while a "0" indicates grandmaternal origin, and "-" indicates that the locus was untyped or uninformative.

TABLE 6

Key Recombinants Used for Genetic Ordering of New STR Loci Developed in Our Laboratory Within the BRCA1 Region of 17q

CEPH Family	ID	M/P	Mfd15	THRA1	MFD191	ED2	AA1	Z109	4-7	YM29	Mfd188	SCG40	42D6
13292	4	M	1	1	1	1	1	0	0	0	0	0	0
13294	4	M	1	0	0	—	0	—	—	—	0	—	—
13294	6	M	0	0	1	—	1	—	—	—	1	—	—
1333	4	M	1	1	1	—	0	—	—	0	0	—	0
1333	6	M	0	0	1	—	1	—	—	1	1	—	1
1333	3	M	0	0	1	—	—	—	1	1	1	—	1

TABLE 7

Kindred 2082 Recombinants

ID	M/P	Mfd15	Mfd191	ED2	AA1	4-7	YM29	Mfd188	SCG40	42D6
63	M	0	0	1	—	1	1	1	1	1
125	M	1	1	1	—	1	1	1	0	0
40	M	1	1	0	—	0	—	0	0	0
22	P	0	0	1	1	1	1	1	1	1

From CEPH 1333-04, we see that AA1 and YM29 must lie distal to Mfd191. From 13292, it can be inferred that both AA1 and ED2 are proximal to 4-7, YM29, and Mfd188. The recombinants found in K2082 provide some additional ordering information. Three independent observations (individual numbers 22, 40, & 63) place AA1, ED2, 4-7, and YM29, and Mfd188 distal to Mfd191, while ID 125 places 4-7, YM29, and Mfd188 proximal to SCG40. No genetic information on the relative ordering within the two clusters of markers AA1/ED2 and 4-7/YM29/Mfd188 was obtained from the genetic recombinant analysis. Although ordering loci with respect to hybrids which are known to contain "holes" in which small pieces of interstitial human DNA may be missing is problematic, the hybrid patterns indicate that 4-7 lies above both YM29 and Mfd188.

EXAMPLE 5

Genetic Analyses of Breast Cancer Kindreds with Markers AA1, 4-7, ED2, and YM29

In addition to the three kindreds containing key recombinants which have been discussed previously, kindred K2039 was shown through analysis of the newly developed STR markers to be linked to the region and to contain a useful recombinant.

Table 8 defines the haplotypes (shown in coded form) of the kindreds in terms of specific marker alleles at each locus and their respective frequencies. In Table 8, alleles are listed in descending order of frequency; frequencies of alleles 1-5 for each locus are given in Table 5. Haplotypes coded H are BRCA1 associated haplotypes, P designates a partial H haplotype, and an R indicates an observable recombinant haplotype. As evident in Table 8, not all kindreds were typed for all markers; moreover, not all individuals within a kindred were typed for an identical set of markers, especially in K2082. With one exception, only haplotypes inherited from affected or at-risk kindred members are shown; haplotypes from spouses marrying into the kindred are not described. Thus in a given sibship, the appearance of haplotypes X and Y indicates that both haplotypes from the affected/at-risk individual were seen and neither was a breast cancer associated haplotype.

TABLE 8

Breast Cancer Linked Haplotypes Found in the Three Kindreds

Kin.	HAP	Mfd15	THRA1	Mfd191	tdj1475	ED2	AA1	Z109	CA375	4-7	YM29	Mfd188	SCG40	6C1	42D6
1901	H1	1	5	5	3	1	4	NI	NI	1	1	3	NI	NI	1
	R2	9	2	5	6	1	4	NI	NI	1	1	3	NI	NI	1
2082	H1	3	NI	4	6	6	1	NI	NI	2	1	4	2	NI	1
	P1	3	NI	4	NI	NI	NI	NI	NI	NI	NI	4	2	NI	1
	P2	3	NI	NI	NI	NI	NI	NI	NI	NI	NI	4	NI	NI	NI
	R1	6	NI	1	5	6	1	NI	NI	2	1	4	2	NI	1
	R2	6	NI	4	6	6	1	NI	NI	2	1	4	2	NI	1
	R3	3	NI	4	NI	6	1	NI	NI	2	1	4	1	NI	7
	R4	7	NI	1	NI	1	5	NI	NI	4	6	1	2	NI	1
	R5	3	NI	4	NI	NI	NI	NI	NI	NI	2	1	NI	NI	NI
	R6	3	NI	4	3	1	2	NI	NI	1	2	2	6	NI	6

TABLE 8-continued

Breast Cancer Linked Haplotypes Found in the Three Kindreds

Kin.	HAP	Mfd15	THRA1	Mfd191	tdj1475	ED2	AA1	Z109	CA375	4-7	YM29	Mfd188	SCG40	6C1	42D6
	R7	3	NI	4	3	7	1	NI	NI	1	1	3	7	NI	4
2035	H1	8	2	1	NI	5	1	1	4	3	1	6	8	2	4
	H2	8	2	1	NI	5	1	1	2	1	1	2	3	1	4
	R2	8	2	1	NI	5	1	1	2	1	1	2	3	6	1

In kindred K1901, the new markers showed no observable recombination with breast cancer susceptibility, indicating that the recombination event in this kindred most likely took place between THRA1 and ED2. Thus, no new BRCA1 localization information was obtained based upon studying the four new markers in this kindred. In kindred 2082 the key recombinant individual has inherited the linked alleles for ED2, 4-7, AA1, and YM29, and was recombinant for tdj1474 indicating that the recombination event occurred in this individual between tdj1474 and ED2/AA1.

There are three haplotypes of interest in kindred K2035, H1, H2, and R2 shown in Table 8. H1 is present in the four cases and one obligate male carrier descendant from individual 17 while H2 is present or inferred in two cases and two obligate male carriers in descendants of individual 10. R2 is identical to H2 for loci between and including Mfd15 and SCG40, but has recombined between SCG40 and 42D6. Since we have established that BRCA1 is proximal to 42D6, this H2/R2 difference adds no further localization information. H1 and R2 share an identical allele at Mfd15, THRA1, AA1, and ED2 but differ for loci presumed distal to ED2, i.e., 4-7, Mfd188, SCG40, and 6C1. Although the two haplotypes are concordant for the 5th allele for marker YM29, a marker which maps physically between 4-7 and Mfd 188, it is likely that the alleles are shared identical by state rather than identical by descent since this allele is the most common allele at this locus with a frequency estimated in CEPH parents of 0.42. By contrast, the linked alleles shared at the Mfd15 and ED2 loci have frequencies of 0.04 and 0.09, respectively. They also share more common alleles at Mfd191 (frequency=0.52), THRA1, and AA1 (frequency=0.28). This is the key recombinant in the set as it is the sole recombinant in which breast cancer segregated with the proximal portion of the haplotype, thus setting the distal boundary. The evidence from this kindred therefore places the BRCA1 locus proximal to 4-7.

The recombination event in kindred 2082 which places BRCA1 distal to tdj1474 is the only one of the four events described which can be directly inferred; that is, the affected mother's genotype can be inferred from her spouse and offspring, and the recombinant haplotype can be seen in her affected daughter. In this family the odds in favor of affected individuals carrying BRCA1 susceptibility alleles are extremely high; the only possible interpretations of the data are that BRCA1 is distal to Mfd191 or alternatively that the purported recombinant is a sporadic case of ovarian cancer at age 44. Rather than a directly observable or inferred recombinant, interpretation of kindred 2035 depends on the observation of distinct 17q-haplotypes segregating in different and sometimes distantly related branches of the kindred. The observation that portions of these haplotypes have alleles in common for some markers while they differ at other markers places the BRCA1 locus in the shared region. The confidence in this placement depends on several factors: the relationship between the individuals carrying the respective haplotypes, the frequency of the shared allele, the certainty with which the haplotypes can be shown to segregate with the BRCA1 locus, and the density of the markers in the region which define the haplotype. In the case of kindred 2035, the two branches are closely related, and each branch has a number of early onset cases which carry the respective haplotype. While two of the shared alleles are common, (Mfd191, THRA1), the estimated frequencies of the shared alleles at Mfd15, AA1, and ED2 are 0.04, 0.28, and 0.09, respectively. It is therefore highly likely that these alleles are identical by descent (derived from a common ancestor) rather than identical by state (the same allele but derived from the general population).

EXAMPLE 6

Refined Physical Mapping Studies Place the BRCA1 Gene in a Region Flanked by tdj1474 and U5R

Since its initial localization to chromosome 17q in 1990 (Hall et al., 1990) a great deal of effort has gone into localizing the BRCA1 gene to a region small enough to allow implementation of effective positional cloning strategies to isolate the gene. The BRCA1 locus was first localized to the interval Mfd15 (D17S250)-42D6 (D17S588) by multipoint linkage analysis (Easton et al., 1993) in the collaborative Breast Cancer Linkage Consortium dataset consisting of 214 families collected worldwide. Subsequent refinements of the localization have been based upon individual recombinant events in specific families. The region THRA1-D17S183 was defined by Bowcock et al., 1993; and the region THRA1-D17S78 was defined by Simard et al., 1993.

We further showed that the BRCA1 locus must lie distal to the marker Mfd191 (D17S776) (Goldgar et al., 1994). This marker is known to lie distal to THRA1 and RARA. The smallest published region for the BRCA1 locus is thus between D17S776 and D17S78. This region still contains approximately 1.5 million bases of DNA, making the isolation and testing of all genes in the region a very difficult task. We have therefore undertaken the tasks of constructing a physical map of the region, isolating a set of polymorphic STR markers located in the region, and analyzing these new markers in a set of informative families to refine the location of the BRCA1 gene to a manageable interval.

Four families provide important genetic evidence for localization of BRCA1 to a sufficiently small region for the application of positional cloning strategies. Two families (K2082, K1901) provide data relating to the proximal boundary for BRCA1 and the other two (K2035, K1813) fix the distal boundary. These families are discussed in detail below. A total of 15 Short Tandem Repeat markers assayable by PCR were used to refine this localization in the families studied. These markers include DS17S7654, DS17S975, tdj1474, and tdj1239. Primer sequences for these markers are provided in SEQ ID NO:3 and SEQ ID NO:4 for

DS17S754; in SEQ ID NO:5 and SEQ ID NO:6 for DS17S975; in SEQ ID NO:7 and SEQ ID NO:8 for tdj1474; and, in SEQ ID NO:9 and SEQ ID NO:10 for tdj1239.

Kindred 2082

Kindred 2082 is the largest BRCA1-linked breast/ovarian cancer family studied to date. It has a LOD score of 8.6, providing unequivocal evidence for 17q linkage. This family has been previously described and shown to contain a critical recombinant placing BRCA1 distal to MFD191 (D17S776). This recombinant occurred in a woman diagnosed with ovarian cancer at age 45 whose mother had ovarian cancer at age 63. The affected mother was deceased; however, from her children, she could be inferred to have the linked haplotype present in the 30 other linked cases in the family in the region between Mfd15 and Mfd188. Her affected daughter received the linked allele at the loci ED2, 4–7, and Mfd188, but received the allele on the non-BRCA1 chromosome at Mfd15 and Mfd91. In order to further localize this recombination breakpoint, we tested DNA from the key members of this family for the following markers derived from physical mapping resources: tdj1474, tdj1239, CF4, D17S855. For the markers tdj1474 and CF4, the affected daughter did not receive the linked allele. For the STR locus tdj1239, however, the mother could be inferred to be informative and her daughter did receive the BRCA1-associated allele. D17S855 was not informative in this family. Based on this analysis, the order is 17q centromere-Mfd191-17HSD-CF4-tdj1474-tdj1239-D17S855-ED2-4–7-Mfd188-17q telomere. The recombinant described above therefore places BRCA1 distal to tdj1474, and the breakpoint is localized to the interval between tdj1474 and tdj1239. The only alternative explanation for the data in this family other than that of BRCA1 being located distal to tdj1474, is that the ovarian cancer present in the recombinant individual is caused by reasons independent of the BRCA1 gene. Given that ovarian cancer diagnosed before age 50 is rare, this alternate explanation is exceedingly unlikely.

Kindred 1901

Kindred 1901 is an early-onset breast cancer family with 7 cases of breast cancer diagnosed before 50, 4 of which were diagnosed before age 40. In addition, there were three cases of breast cancer diagnosed between the ages of 50 and 70. One case of breast cancer also had ovarian cancer at age 61. This family currently has a LOD score of 1.5 with D17S855. Given this linkage evidence and the presence of at lease one ovarian cancer case, this family has a posterior probability of being due to BRCA1 of over 0.99. In this family, the recombination comes from the fact that an individual who is the brother of the ovarian cancer case from which the majority of the other cases descend, only shares a portion of the haplotype which is cosegregating with the other cases in the family. However, he passed this partial haplotype to his daughter who developed breast cancer at age 44. If this case is due to the BRCA1 gene, then only the part of the haplotype shared between this brother and his sister can contain the BRCA1 gene. The difficulty in interpretation of this kind of information is that while one can be sure of the markers which are not shared and therefore recombinant, markers which are concordant can either be shared because they are non-recombinant, or because their parent was homozygous. Without the parental genotypic data it is impossible to discriminate between these alternatives. Inspection of the haplotype in K1901, shows that he does not share the linked allele at Mfd15 (D17S250), THRA1, CF4 (D17S1320), and tdj1474 (17DS1321). He does share the linked allele at Mfd191 (D17S776), ED2 (D17S1327), tdj1239 (D17S1328), and Mfd188 (D17S579).

Although the allele shared at Mfd191 is relatively rare (0.07), we would presume that the parent was homozygous since they are recombinant with markers located nearby on either side, and a double recombination event in this region would be extremely unlikely. Thus the evidence in this family would also place the BRCA1 locus distal to tdj474. However, the lower limit of this breakpoint is impossible to determine without parental genotype information. It is intriguing that the key recombinant breakpoint in this family confirms the result in Kindred 2082. As before, the localization information in this family is only meaningful if the breast cancer was due to the BRCA1 gene. However, her relatively early age at diagnosis (44) makes this seem very likely since the risk of breast cancer before age 45 in the general population is low (approximately 1%).

Kindred 2035

This family is similar to K1901 in that the information on the critical recombinant events is not directly observed but is inferred from the observation that the two haplotypes which are cosegregating with the early onset breast cancer in the two branches of the family appear identical for markers located in the proximal portion of the 17q BRCA1 region but differ at more distal loci. Each of these two haplotypes occurs in at least four cases of early-onset or bilateral breast cancer. The overall LOD score with ED2 in this family is 2.2, and considering that there is a case of ovarian cancer in the family (indicating a prior probability of BRCA1 linkage of 80%), the resulting posterior probability that this family is linked to BRCA1 is 0.998. The haplotypes are identical for the markers Mfd15, THRA1, Mfd191, ED2, AA1, D17S858 and D17S902. The common allele at Mfd15 and ED2 are both quite rare, indicating that this haplotype is shared identical by descent. The haplotypes are discordant, however, for CA375, 4–7, and Mfd188, and several more distal markers. This indicates that the BRCA1 locus must lie above the marker CA-375. This marker is located approximately 50 kb below D17S78, so it serves primarily as additional confirmation of this previous lower boundary as reported in Simard et al. (1993).

Kindred 1813

Kindred 1813 is a small family with four cases of breast cancer diagnosed at very early ages whose mother also had breast cancer diagnosed at an early age and ovarian cancer some years later. This family yields a maximum multipoint LOD score of 0.60 with 17q markers and, given that there is at least one case of ovarian cancer, results in a posterior probability of being a BRCA1 linked family of 0.93. This family contains a directly observable recombination event in individual 18 (see FIG. 5 in Simard et al., *Human Mol. Genet.* 2:1193–1199 (1993)), who developed breast cancer at age 34. The genotype of her affected mother at the relevant 17q loci can be inferred from her genotypes, her affected sister's genotypes, and the genotypes of three other unaffected siblings. Individual 18 inherits the BRCA1-linked alleles for the following loci: Mfd15, THRA1, D17S800, D17S855, AA1, and D17S931. However, for markers below D17S931, i.e., U5R, vrs31, D17S858, and D17S579, she has inherited the alleles located on the non-disease bearing chromosome. The evidence from this family therefore would place the BRCA1 locus proximal to the marker U5R. Because of her early age at diagnosis (34) it is extremely unlikely that the recombinant individual's cancer is not due to the gene responsible for the other cases of breast/ovarian cancer in this family; the uncertainty in this family comes from our somewhat smaller amount of evidence that breast cancer in this family is due to BRCA1 rather than a second, as yet unmapped, breast cancer susceptibility locus.

Size of the region containing BRCA1

Based on the genetic data described in detail above, the BRCA1 locus must lie in the interval between the markers tdj1474 and U5R, both of which were isolated in our laboratory. Based upon the physical maps shown in FIGS. 2 and 3, we can try to estimate the physical distance between these two loci. It takes approximately 14 P1 clones with an average insert size of approximately 80 kb to span the region. However, because all of these P1s overlap to some unknown degree, the physical region is most likely much smaller than 14 times 80 kb. Based on restriction maps of the clones covering the region, we estimate the size of the region containing BRCA1 to be approximately 650 kb.

EXAMPLE 7

Identification of Candidate cDNA Clones for the BRCA1 Locus by Genomic Analysis of the Contig Region

Complete screen of the plausible region. The first method to identify candidate cDNAs, although labor intensive, used known techniques. The method comprised the screening of cosmids and P1 and BAC clones in the contig to identify putative coding sequences. The clones containing putative coding sequences were then used as probes on filters of cDNA libraries to identify candidate cDNA clones for future analysis. The clones were screened for putative coding sequences by either of two methods.

Zoo blots. The first method for identifying putative coding sequences was by screening the cosmid and P1 clones for sequences conserved through evolution across several species. This technique is referred to as "zoo blot analysis" and is described by Monaco, 1986. Specifically, DNAs from cow, chicken, pig, mouse and rat were digested with the restriction enzymes EcoRI and HindIII (8 µg of DNA per enzyme). The digested DNAs were separated overnight on an 0.7% gel at 20 volts for 16 hours (14 cm gel), and the DNA transferred to Nylon membranes using standard Southern blot techniques. For example, the zoo blot filter was treated at 65° C. in 0.1× SSC, 0.5% SDS, and 0.2M Tris, pH 8.0, for 30 minutes and then blocked overnight at 42° C. in 5× SSC, 10% PEG 8000, 20 mM $NaPO_4$ pH 6.8, 100 µg/ml Salmon Sperm DNA, 1x Denhardt's, 50% formamide, 0.1% SDS, and 2 µg/ml C_ot-1 DNA.

The cosmid and P1 clones to be analyzed were digested with a restriction enzyme to release the human DNA from the vector DNA. The DNA was separated on a 14 cm, 0.5% agarose gel run overnight at 20 volts for 16 hours. The human DNA bands were cut out of the gel and electroeluted from the gel wedge at 100 volts for at least two hours in 0.5x Tris Acetate buffer (Maniatis et al., 1982). The eluted Not I digested DNA (~15 kb to 25 kb) was then digested with EcoRI restriction enzyme to give smaller fragments (~0.5 kb to 5.0 kb) which melt apart more easily for the next step of labeling the DNA with radionucleotides. The DNA fragments were labeled by means of the hexamer random prime labeling method (Boehringer-Mannheim, Cat. #1004760). The labeled DNA was spermine precipitated (add 100 µl TE, 5 µl 0.1M spermine, and 5 µl of 10 mg/ml salmon sperm DNA) to remove unincorporated radionucleotides. The labeled DNA was then resuspended in 100 µl TE, 0.5M NaCl at 65° C. for 5 minutes and then blocked with Human C_ot-1 DNA for 2–4 hrs. as per the manufacturer's instructions (Gibco/BRL, Cat. #5279SA). The C_ot-1 blocked probe was incubated on the zoo blot filters in the blocking solution overnight at 42° C. The filters were washed for 30 minutes at room temperature in 2× SSC, 0.1% SDS, and then in the same buffer for 30 minutes at 55° C. The filters were then exposed 1 to 3 days at −70° C. to Kodak XAR-5 film with an intensifying screen. Thus, the zoo blots were hybridized with either the pool of Eco-R1 fragments from the insert, or each of the fragments individually.

HTF island analysis. The second method for identifying cosmids to use as probes on the cDNA libraries was HTF island analysis. Since the pulsed-field map can reveal HTF islands, cosmids that map to these HTF island regions were analyzed with priority. HTF islands are segments of DNA which contain a very high frequency of unmethylated CpG dinucleotides (Tonolio et al., 1990) and are revealed by the clustering of restriction sites of enzymes whose recognition sequences include CpG dinucleotides. Enzymes known to be useful in HTF-island analysis are AscI, NotI, BssHII, EagI, SacII, NaeI, NarI, SmaI, and MluI (Anand, 1992). A pulsed-field map was created using the enzymes NotI, NruI, EagI, SacII, and SalI, and two HTF islands were found. These islands are located in the distal end of the region, one being distal to the GP2B locus, and the other being proximal to the same locus, both outside the BRCA1 region. The cosmids derived from the YACs that cover these two locations were analyzed to identify those that contain these restriction sites, and thus the HTF islands.

cDNA screening. Those clones that contain HTF islands or show hybridization to other species DNA besides human are likely to contain coding sequences. The human DNA from these clones was isolated as whole insert or as EcoR1 fragments and labeled as described above. The labeled DNA was used to screen filters of various cDNA libraries under the same conditions as the zoo blots except that the cDNA filters undergo a more stringent wash of 0.1× SSC, 0.1% SDS at 65° C. for 30 minutes twice.

Most of the cDNA libraries used to date in our studies (libraries from normal breast tissue, breast tissue from a woman in her eighth month of pregnancy and a breast malignancy) were prepared at Clonetech, Inc. The cDNA library generated from breast tissue of an 8 month pregnant woman is available from Clonetech (Cat. #HL1037a) in the Lambda gt-10 vector, and is grown in C600Hfl bacterial host cells. Normal breast tissue and malignant breast tissue samples were isolated from a 37 year old Caucasian female and one-gram of each tissue was sent to Clonetech for mRNA processing and cDNA library construction. The latter two libraries were generated using both random and oligo-dT priming, with size selection of the final products which were then cloned into the Lambda Zap II vector, and grown in XL1-blue strain of bacteria as described by the manufacturer. Additional tissue-specific cDNA libraries include human fetal brain (Stratagene, Cat. 936206), human testis (Clonetech Cat. HL3024), human thymus (Clonetech Cat. HL 1127n), human brain (Clonetech Cat. HL11810), human placenta (Clonetech Cat 1075b), and human skeletal muscle (Clonetech Cat. HL1124b).

The cDNA libraries were plated with their host cells on NZCYM plates, and filter lifts are made in duplicate from each plate as per Maniatis et al. (1982). Insert (human) DNA from the candidate genomic clones was purified and radioactively labeled to high specific activity. The radioactive DNA was then hybridized to the cDNA filters to identify those cDNAs which correspond to genes located within the candidate cosmid clone. cDNAs identified by this method were picked, replated, and screened again with the labeled clone insert or its derived EcoR1 fragment DNA to verify their positive status. Clones that were positive after this second round of screening were then grown up and their DNA purified for Southern blot analysis and sequencing.

Clones were either purified as plasmid through in vivo excision of the plasmid from the Lambda vector as described in the protocols from the manufacturers, or isolated from the Lambda vector as a restriction fragment and subcloned into plasmid vector.

The Southern blot analysis was performed in duplicate, one using the original genomic insert DNA as a probe to verify that cDNA insert contains hybridizing sequences. The second blot was hybridized with cDNA insert DNA from the largest cDNA clone to identify which clones represent the same gene. All cDNAs which hybridize with the genomic clone and are unique were sequenced and the DNA analyzed to determine if the sequences represent known or unique genes. All cDNA clones which appear to be unique were further analyzed as candidate BRCA1 loci. Specifically, the clones are hybridized to Northern blots to look for breast specific expression and differential expression in normal versus breast tumor RNAs. They are also analyzed by PCR on clones in the BRCA1 region to verify their location. To map the extent of the locus, full length cDNAs are isolated and their sequences used as PCR probes on the YACs and the clones surrounding and including the original identifying clones. Intron-exon boundaries are then further defined through sequence analysis.

We have screened the normal breast, 8 month pregnant breast and fetal brain cDNA libraries with zoo blot-positive Eco R1 fragments from cosmid BAC and P1 clones in the region. Potential BRCA1 cDNA clones were identified among the three libraries. Clones were picked, replated, and screened again with the original probe to verify that they were positive.

Analysis of hybrid-selected cDNA. cDNA fragments obtained from direct selection were checked by Southern blot hybridization against the probe DNA to verify that they originated from the contig. Those that passed this test were sequenced in their entirety. The set of DNA sequences obtained in this way were then checked against each other to find independent clones that overlapped. For example, the clones 694-65, 1240-1 and 1240-33 were obtained independently and subsequently shown to derive from the same contiguous cDNA sequence which has been named EST:489:1.

Analysis of candidate clones. One or more of the candidate genes generated from above were sequenced and the information used for identification and classification of each expressed gene. The DNA sequences were compared to known genes by nucleotide sequence comparisons and by translation in all frames followed by a comparison with known amino acid sequences. This was accomplished using Genetic Data Environment (GDE) version 2.2 software and the Basic Local Alignment Search Tool (Blast) series of client/server software packages (e.g., BLASTN 1.3.1 3MP), for sequence comparison against both local and remote sequence databases (e.g., GenBank), running on Sun SPARC workstations. Sequences reconstructed from collections of cDNA clones identified with the cosmids and P1s have been generated. All candidate genes that represented new sequences were analyzed further to test their candidacy for the putative BRCA1 locus.

Mutation screening. To screen for mutations in the affected pedigrees, two different approaches were followed. First, genomic DNA isolated from family members known to carry the susceptibility allele of BRCA1 was used as a template for amplification of candidate gene sequences by PCR. If the PCR primers flank or overlap an intron/exon boundary, the amplified fragment will be larger than predicted from the cDNA sequence or will not be present in the amplified mixture. By a combination of such amplification experiments and sequencing of P1, BAC or cosmid clones using the set of designed primers it is possible to establish the intron/exon structure and ultimately obtain the DNA sequences of genomic DNA from the pedigrees.

A second approach that is much more rapid if the intron/exon structure of the candidate gene is complex involves sequencing fragments amplified from pedigree lymphocyte cDNA. CDNA synthesized from lymphocyte mRNA extracted from pedigree blood was used as a substrate for PCR amplification using the set of designed primers. If the candidate gene is expressed to a significant extent in lymphocytes, such experiments usually produce amplified fragments that can be sequenced directly without knowledge of intron/exon junctions.

The products of such sequencing reactions were analyzed by gel electrophoresis to determine positions in the sequence that contain either mutations such as deletions or insertions, or base pair substitutions that cause amino acid changes or other detrimental effects.

Any sequence within the BRCA1 region that is expressed in breast is considered to be a candidate gene for BRCA1. Compelling evidence that a given candidate gene corresponds to BRCA1 comes from a demonstration that pedigree families contain defective alleles of the candidate.

EXAMPLE 8

Identification of BRCA1

Identification of BRCA1. Using several strategies, a detailed map of transcripts was developed for the 600 kb region of 17q21 between D17S1321 and D17S1324. Candidate expressed sequences were defined as DNA sequences obtained from: 1) direct screening of breast, fetal brain, or lymphocyte cDNA libraries, 2) hybrid selection of breast, lymphocyte or ovary cDNAs, or 3) random sequencing of genomic DNA and prediction of coding exons by XPOUND (Thomas and Skolnick, 1994). These expressed sequences in many cases were assembled into contigs composed of several independently identified sequences. Candidate genes may comprise more than one of these candidate expressed sequences. Sixty-five candidate expressed sequences within this region were identified by hybrid selection, by direct screening of cDNA libraries, and by random sequencing of P1 subclones. Expressed sequences were characterized by transcript size, DNA sequence, database comparison, expression pattern, genomic structure, and, most importantly, DNA sequence analysis in individuals from kindreds segregating 17q-linked breast and ovarian cancer susceptibility.

Three independent contigs of expressed sequence, 1141:1 (649 bp), 694:5 (213 bp) and 754:2 (1079 bp) were isolated and eventually shown to represent portions of BRCA1. When ESTs for these contigs were used as hybridization probes for Northern analysis, a single transcript of approximately 7.8 kb was observed in normal breast mRNA, suggesting that they encode different portions of a single gene. Screens of breast, fetal brain, thymus, testes, lymphocyte and placental cDNA libraries and PCR experiments with breast mRNA linked the 1141:1, 694:5 and 754:2 contigs. 5' RACE experiments with thymus, testes, and breast mRNA extended the contig to the putative 5' end, yielding a composite full length sequence. PCR and direct sequencing of P1s and BACs in the region were used to identify the location of introns and allowed the determination of splice donor and acceptor sites. These three expressed sequences were merged into a single transcription unit that proved in the final analysis to be BRCA1. This transcription unit is located adjacent to D17S855 in the center of the 600 kb region (FIG. 4).

Combination of sequences obtained from cDNA clones, hybrid selection sequences, and amplified PCR products allowed construction of a composite full length BRCA1 cDNA (SEQ ID NO:1). The sequence of the BRCA1 cDNA (up through the stop codon) has also been deposited with GenBank and assigned accession number U-14680. This deposited sequence is incorporated herein by reference. The cDNA clone extending farthest in the 3' direction contains a poly(A) tract preceded by a polyadenylation signal. Conceptual translation of the cDNA revealed a single long open reading frame of 208 kilodaltons (amino acid sequence: SEQ ID NO:2) with a potential initiation codon flanked by sequences resembling the Kozak consensus sequence (Kozak, 1987). Smith-Waterman (Smith and Waterman, 1981) and BLAST (Altschul et al., 1990) searches identified a sequence near the amino terminus with considerable homology to zinc-finger domains (FIG. 5). This sequence contains cysteine and histidine residues present in the consensus C3HC4 zinc-finger motif and shares multiple other residues with zinc-finger proteins in the databases. The BRCA1 gene is composed of 23 coding exons arrayed over more than 100 kb of genomic DNA (FIG. 6). Northern blots using fragments of the BRCA1 cDNA as probes identified a single transcript of about 7.8 kb, present most abundantly in breast, thymus and testis, and also present in ovary (FIG. 7). Four alternatively spliced products were observed as independent cDNA clones; 3 of these were detected in breast and 2 in ovary mRNA (FIG. 6). A PCR survey from tissue cDNAs further supports the idea that there is considerable heterogeneity near the 5' end of transcripts from this gene; longest deletion being 1,155 bp. The predominant form of the BRCA1 protein in breast and ovary lacks exon 4. The nucleotide sequence for BRCA1 exon 4 is shown in SEQ ID NO:11, with the predicted amino acid sequence shown in SEQ ID NO:12.

Additional 5' sequence of BRCA1 genomic DNA is set forth in SEQ ID NO:13. The G at position 1 represents the potential start site in testis. The A in position 140 represents the potential start site in somatic tissue. There are six alternative splice forms of this 5' sequence as shown in FIG. 8. The G at position 356 represents the canonical first splice donor site. The G at position 444 represents the first splice donor site in two clones (testis 1 and testis 2). The G at position 889 represents the first splice donor site in thymus 3. A fourth splice donor site is the G at position 1230. The T at position 1513 represents the splice acceptor site for all of the above splice donors. A fifth alternate splice form has a first splice donor site at position 349 with a first acceptor site at position 591 and a second splice donor site at position 889 and a second acceptor site at position 1513. A sixth alternate form is unspliced in this 5' region. The A at position 1532 is the canonical start site, which appears at position 120 of SEQ ID NO:1. Partial genomic DNA sequences determined for BRCA1 are set forth in FIGS. 10A–10H and SEQ ID Numbers:14–34. The lower case letters (in FIGS. 10A–10H) denote intron sequence while the upper case letters denote exon sequence. Indefinite intervals within introns are designated with vvvvvvvvvvvvv in FIGS. 10A–10H. The intron/exon junctions are shown in Table 9. The CAG found at the 5' end of exons 8 and 14 is found in some cDNAs but not in others. Known polymorphic sites are shown in FIGS. 10A–10H in boldface type and are underlined.

TABLE 9

Exon	Base Position*			Intron Borders	
No.	5'	3'	Length	5'	3'
e1	1	100	100	GATAAATTAAAACTGCGACTGCGCGGCGTG[35]**	GTAGTAGAGTCCCGGGAAAGGGACAGGGGG[36]
e2	101	199	99	ATATATATATGTTTTTCTAATGTGTTAAAG[37]	GTAAGTCAGCACAAGAGTGTATTAATTTGG[38]
e3	200	253	54	TTTCTTTTTCTCCCCCCCCTACCCTGCTAG[39]	GTAAGTTTGAATGTGTTATGTGGCTCCATT[40]
e4	***	***	111	AGCTACTTTTTTTTTTTTTTTTTGAGACAG[41]	GTAAGTGCACACCACCATATCCAGCTAAAT[42]
e5	254	331	78	AATTGTTCTTTCTTTCTTTATAATTTATAG[43]	GTATATAATTTGGTAATGATGCTAGGTTGG[44]
e6	332	420	89	GAGTGTGTTTCTCAAACAATTTAATTTCAG[45]	GTAAGTGTTGAATATCCCAAGAATCACACT[46]
e7	421	560	140	AAACATAATGTTTTCCCTTGTATTTTACAG[47]	GTAAAACCATTTGTTTTCTTCTTCTTCTTC[48]
e8	561	666	106	TGCTTGACTGTTCTTTACCATACTGTTTAG[49]	GTAAGGGTCTCAGGTTTTTTAAGTATTTAA[50]
e9	667	712	46	TGATTTATTTTTTGGGGGGAAATTTTTTAG[51]	GTGAGTCAAAGAGAACCTTTGTCTATGAAG[52]
e10	713	789	77	TCTTATTAGGACTCTGTCTTTTCCCTATAG[53]	GTAATGGCAAAGTTTGCCAACTTAACAGGC[54]
e11	790	4215	3426	GAGTACCTTGTTATTTTTGTATATTTTCAG[55]	GTATTGGAACCAGGTTTTTGTGTTTGCCCC[56]
e12	4216	4302	87	ACATCTGAACCTCTGTTTTTGTTATTTAAG[57]	AGGTAAAAAGCGTGTGTGTGTGTGCACATG[58]
e13	4303	4476	174	CATTTTCTTGGTACCATTTATCGTTTTTGA[59]	GTGTGTATTGTTGGCCAAACACTGATATCT[60]
e14	4477	4603	127	AGTAGATTTGTTTTCTCATTCCATTTAAAG[61]	GTAAGAAACATCAATGTAAAGATGCTGTGG[62]
e15	4604	4794	191	ATGGTTTTCTCCTTGCATTTATCTTTCTAG[63]	GTAATATTTCATCTGCTGTATTGGAACAAA[64]
e16	4795	5105	311	TGTAAATTAAACTTCTCCCATTCCTTTCAG[65]	GTGAGTGTATCCATATGTATCTCCCTAATG[66]
e17	5106	5193	88	ATGATAATGGAATATTTGATTTAATTTCAG[67]	GTATACCAAGAACCTTTACAGAATACCTTG[68]
e18	5194	5271	78	CTAATCCTTTGAGTGTTTTTCATTCTGCAG[69]	GTAAGTATAATACTATTTCTCCCCTCCTCC[70]
e19	5272	5312	41	TGTAACCTGTCTTTTCTATGATCTCTTTAG[71]	GTAAGTACTTGATGTTACAAACTAACCAGA[72]
e20	5313	5396	84	TCCTGATGGGTTGTGTTTGGTTTCTTTCAG[73]	GTAAAGCTCCCTCCCTCAAGTTGACAAAAA[74]
e21	5397	5451	55	CTGTCCCTCTCTCTTCCTCTCTTCTTCCAG[75]	GTAAGAGCCTGGGAGAACCCCAGAGTTCCA[76]
e22	5452	5525	74	AGTGATTTTACATGTAAATGTCCATTTTAG[77]	GTAAGTATTGGGTGCCCTGTCAGTGTGGGA[78]
e23	5526	5586	61	TTGAATGCTCTTTCCTTCCTGGGGATCCAG[79]	GTAAGGTGCCTCGCATGTACCTGTGCTATT[80]
e24	5587	5914	328	CTAATCTCTGCTTGTGTTCTCTGTCTCCAG[81]	

*Base numbers in SEQ ID NO: 1.

**Numbers in superscript refer to SEQ ID NOS.

***e4 from SEQ ID NO: 11.

the molecular basis for the heterogeneity involves differential choice of the first splice donor site, and the changes detected all alter the transcript in the region 5' of the identified start codon. We have detected six potential alternate splice donors in this 5' untranslated region, with the

Low stringency blots in which genomic DNA from organisms of diverse phylogenetic background were probed with BRCA1 sequences that lack the zinc-finger region revealed strongly hybridizing fragments in human, monkey, sheep and pig, and very weak hybridization signals in rodents. This result indicates that, apart from the zinc-finger domain, BRCA1 is conserved only at a moderate level through evolution.

Germline BRCA1 mutations in 17q-linked kindreds. The most rigorous test for BRCA1 candidate genes is to search for potentially disruptive mutations in carrier individuals from kindreds that segregate 17q-linked susceptibility to breast and ovarian cancer. Such individuals must contain BRCA1 alleles that differ from the wildtype sequence. The set of DNA samples used in this analysis consisted of DNA from individuals representing 8 different BRCA1 kindreds (Table 10).

TABLE 10

KINDRED DESCRIPTIONS AND ASSOCIATED LOD SCORES

	Cases (n)			Sporadic Cases[1]	LOD	
Kindred	Br	Br < 50	Ov	(n)	Score	Markers(s)
2082	31	20	22	7	9.49	D17S1327
2099	22	14	2[3]	0	2.36	D17S800/D17S855[2]
2035	10	8	1[3]	0	2.25	D17S1327
1901	10	7	1[3]	0	1.50	D17S855
1925	4	3	0	0	0.55	D17S579
1910	5	4	0	0	0.36	D17S579/D17S250[2]
1927	5	4	0	1	-0.44	D17S250
1911	8	5	0	2	-0.20	D17S250

[1] Number of women with breast cancer (diagnosed under age 50) or ovarian cancer (diagnosed at any age) who do not share the BRCA1-linked haplotype segregating in the remainder of the cases in the kindred.
[2] Multipoint LOD score calculated using both markers.
[3] Kindred contains one individual who had both breast and ovarian cancer; this individual is counted as a breast cancer case and as an ovarian cancer case.

The logarithm of the odds (LOD) scores in these kindreds range from 9.49 to -0.44 for a set of markers in 17q21. Four of the families have convincing LOD scores for linkage, and 4 have low positive or negative LOD scores. The latter kindreds were included because they demonstrate haplotype sharing at chromosome 17q21 for at least 3 affected members. Furthermore, all kindreds in the set display early age of breast cancer onset and 4 of the kindreds include at least one case of ovarian cancer, both hallmarks of BRCA1 kindreds. One kindred, 2082, has nearly equal incidence of breast and ovarian cancer, an unusual occurrence given the relative rarity of ovarian cancer in the population. All of the kindreds except two were ascertained in Utah. K2035 is from the midwest. K2099 is an African-American kindred from the southern USA.

In the initial screen for predisposing mutations in BRCA1, DNA from one individual who carries the perdisposing haplotype in each kindred was tested. The 23 coding exons and associated splice junction were amplified either from genomic DNA samples or from cDNA prepared from lymphocyte mRNA. When the amplified DNA sequences were compared to the wildtype sequence, 4 of the 8 kindred samples were found to contain sequence variants (Table 11).

TABLE 11

PREDISPOSING MUTATIONS

Kindred Number	Mutation	Coding Effect	Location*
2082	C → T	Gln → Stop	4056
1910	extra C	frameshift	5385
2099	T → G	Met → Arg	5443
2035	?	loss of transcript	
1901	11 bp deletion	frameshift	189

*In Sequence ID NO: 1

All four sequence variants are heterozygous and each appears in only one of the kindreds. Kinderd 2082 contains a nonsense mutation in exon 11 (FIG. 9A). Kindred 1910 contains a single nucleoting insertion in exon 20 (FIG. 9B), and Kindred 2099 contains a missense mutation in exon 21, resulting in a Met→Arg substitution. The frameshift and nonsense mutations are likely disruptive to the function of the BRCA1 product. The peptide encoded by the frameshift allele in Kindred 1910 would contain an altered amino acid sequence beginning 108 residues from the wildtype C-terminus. The peptide encoded by the frameshift allele in Kindred 1901 would contain an altered amino acid sequence beginning with the 24th residue from the wildtype N-terminus. The mutant allele in Kindred 2082 would encode a protein missing 551 residues from the C-terminus. The missense substitution observed in Kindred 2099 is potentially disruptive as it causes the replacement of a small hydrophobic amino acid (Met), by a large charged residue (Arg). Eleven common polymorphisms were also identified, 8 in coding sequence and 3 in introns.

The individual studied in Kindred 2035 evidently contains a regulatory mutation in BRCA 1. In her cDNA, a polymorphic site (A→G at base 3667) appeared homozygous, whereas her genomic DNA revealed heterozygosity at this position (FIG. 9C). A possible explanation for this observation is that mRNA from her mutated BRCA1 allele is absent due to a mutation that affects its production or stability. This possibility was explored further by examining 5 polymorphic sites in the BRCA1 coding region, which are separated by as much as 3.5 kb in the BRCA1 transcript. In all cases where her genomic DNA appeared heterozygous for a polymorphism, cDNA appeared homozygous. In individuals from other kindreds and in non-haplotype carriers in Kindred 2035, these polymorphic sites could be observed as heterozygous in cDNA, implying that amplification from cDNA was not biased in favor of one allele. This analysis indicates that a BRCA1 mutation in Kindred 2035 either prevents transcription or causes instability or aberrant splicing of the BRCA1 transcript.

Cosegregation of BRCA1 mutations with BRCA1haplotypes and population frequency analysis. In addition to potentially disrupting protein function, two criteria must be met for a sequence variant to qualify as a candidate predisposing mutation. The variant must: 1) be present in individuals from the kindred who carry the predisposing BRCA 1 haplotype and absent in other members of the kindred, and 2) be rare in the general population.

Each mutation was tested for cosegregation with BRCA1. For the frameshift mutation in Kindred 1910, two other haplotype carriers and one non-carrier were sequenced (FIG. 9B). Only the carriers exhibited the frameshift mutation. The C to T change in Kindred 2082 created a new AvrII restriction site. Other carriers and non-carriers in the kindred were tested for the presence of the restriction site (FIG. 9A). An allele-specific oligonucleotide (ASO) was designed to detect the presence of the sequence variant in Kindred 2099. Several individuals from the kindred, some known to carry the haplotype associated with the predisposing allele, and others known not to carry the associated haplotype, were screened by ASO for the mutation previously detected in the kindred. In each kindred, the corresponding mutant allele was detected in individuals carrying the BRCA1-associated haplotype, and was not detected in noncaitiers. In the case of the potential regulatory mutation observed in the individual from Kindred 2035, cDNA and genomic DNA from carriers in the kindred were compared for heterozygosity at polymorphic sites. In every instance, the extinguished allele in the cDNA sample was shown to lie on the chromosome that carries the BRCA1 predisposing allele (FIG. 9C).

To exclude the possibility that the mutations were simply common polymorphisms in the population, ASOs for each mutation were used to screen a set of normal DNA samples. Gene frequency estimates in Caucasians were based on random samples from the Utah population. Gene frequency estimates in African-Americans were based on 39 samples provided by M. Peracek-Vance which originate from African-Americans used in her linkage studies and 20 newborn Utah African-Americans. None of the 4 potential predisposing mutations was found in the appropriate control population, indicating that they are rare in the general population. Thus, two important requirements for BRCA1 susceptibility alleles were fulfilled by the candidate predisposing mutations: 1) cosegregation of the mutant allele with disease, and 2) absence of the mutant allele in controls, indicating a low gene frequency in the general population.

Phenotvpic Expression of BRCA1 Mutations. The effect of the mutations on the BRCA1 protein correlated with differences in the observed phenotypic expression in the BRCA1 kindreds. Most BRCA 1 kindreds have a moderately increased ovarian cancer risk, and a smaller subset have high risks of ovarian cancer, comparable to those for breast cancer (Easton et al., 1993). Three of the four kindreds in which BRCA1 mutations were detected fall into the former category, while the fourth (K2082) falls into the high ovarian cancer risk group. Since the BRCA1 nonsense mutation found in K2082 lies closer to the amino terminus than the other mutations detected, it might be expected to have a different phenotype. In fact, Kindred K2082 mutation has a high incidence of ovarian cancer, and a later mean age at diagnosis of breast cancer cases than the other kindreds (Goldgar et al., 1994). This difference in age of onset could be due to an ascertainment bias in the smaller, more highly penetrant families, or it could reflect tissue-specific differences in the behavior of BRCA1 mutations. The other 3 kindreds that segregate known BRCA1 mutations have, on average, one ovarian cancer for every 10 cases of breast cancer, but have a high proportion of breast cancer cases diagnosed in their late 20's or early 30's. Kindred 1910, which has a frameshift mutation, is noteworthy because three of the four affected individuals had bilateral breast cancer, and in each case the second tumor was diagnosed within a year of the first occurrence. Kindred 2035, which segregates a potential regulatory BRCA1 mutation, might also be expected to have a dramatic phenotype. Eighty percent of breast cancer cases in this kindred occur under age 50. This figure is as high as any in the set, suggesting a BRCA1 mutant allele of high penetrance (Table 10).

Although the mutations described above clearly are deleterious, causing breast cancer in women at very young ages, each of the four kindreds with mutations includes at least one woman who carries the mutation who lived until age 80 without developing a malignancy. It will be of utmost importance in the studies that follow to identify other genetic or environmental factors that may ameliorate the effects of BRCA1 mutations.

In four of the eight putative BRCA1-linked kindreds, potential predisposing mutations were not found. Three of these four have LOD scores for BRCA1-linked markers of less than 0.55. Thus, these kindreds may not in reality segregate BRCA1 predisposing alleles. Alternatively, the mutations in these four kindreds may lie in regions of BRCA1 that, for example, affect the level of transcript and therefore have thus far escaped detection.

Role of BRCA1 in Cancer. Most tumor suppressor genes identified to date give rise to protein products that are absent, nonfunctional, or reduced in function. The majority of TP53 mutations are missense; some of these have been shown to produce abnormal p53 molecules that interfere with the function of the wildtype product (Shaulian el al., 1992; Srivastava et al., 1993). A similar dominant negative mechanism of action has been proposed for some adenomatous polyposis coli (APC) alleles that produce truncated molecules (Su et al., 1993), and for point mutations in the Wilms' tumor gene (WT1) that alter DNA binding of the protein (Little et al., 1993). The nature of the mutations observed in the BRCA1 coding sequence is consistent with production of either dominant negative proteins or nonfunctional proteins. The regulatory mutation inferred in Kindred 2035 cannot be a dominant negative; rather, this mutation likely causes reduction or complete loss of BRCA1 expression from the affected allele.

The BRCA1 protein contains a C_3HC_4 zinc-finger domain, similar to those found in numerous DNA binding proteins and implicated in zinc-dependent binding to nucleic acids. The first 180 amino acids of BRCA1 contain five more basic residues than acidic residues. In contrast, the remainder of the molecule is very acidic, with a net excess of 70 acidic residues. The excess negative charge is particularly concentrated near the C-terminus. Thus, one possibility is that BRCA1 encodes a transcription factor with an N-terminal DNA binding domain and a C-terminal transactivational "acidic blob" domain. Interestingly, another familial tumor suppressor gene, WT1, also contains a zinc-finger motif (Haber el al., 1990)). Many cancer predisposing mutations in WT1 alter zinc-finger domains (Little et al., 1993; Haber et al., 1990; Little et al., 1992). WT1 encodes a transcription factor, and alternative splicing of exons that encode parts of the zinc-finger domain alter the DNA binding properties of WT1 (Bickmore et al., 1992). Some alternatively spliced forms of WT1 mRNA generate molecules that act as transcriptional repressors (Drummond et al., 1994). Some BRCA1 splicing variants may alter the zinc-finger motif, raising the possibility that a regulatory mechanism similar to 10 that which occurs in WT1 may apply to BRCA1.

EXAMPLE 9

Analysis of Tumors for BRCA1 Mutations

To focus the analysis on tumors most likely to contain BRCA1 mutations, primary breast and ovarian carcinomas were typed for LOH in the BRCA1 region. Three highly polymorphic, simple tandem repeat markers were used to assess LOH: D17S1323 and D17S855, which are intragenic to BRCA1, and D17S1327, which lies approximately 100 kb distal to BRCA1 . The combined LOH frequency in informative cases (i.e., where the germline was heterozygous) was 32/72 (44%) for the breast carcinomas and 12/21 (57%) for the ovarian carcinomas, consistent with previous measurements of LOH in the region (Futreal et al., 1992b; Jacobs et al., 1993; Sato et al., 1990; Eccles et al., 1990; Cropp et al., 1994). The analysis thus defined a panel of 32 breast tumors and 12 ovarian tumors of mixed race and age of onset to be examined for BRCA mutations. The complete 5,589 bp coding region and intron/exon boundary sequences of the gene were screened in this tumor set by direct sequencing alone or by a combination of single-strand conformation analysis (SSCA) and direct sequencing.

A total of six mutations (of which two are identical) was found, one in an ovarian tumor, four in breast tumors and one in a male unaffected haplotype carrier (Table 12). One mutation, Glu 1541Ter, introduced a stop codon that would create a truncated protein missing 323 amino acids at the carboxy terminus. In addition, two missense mutations were identified. These are Ala1708Glu and Met1775Arg and involve substitutions of small, hydrophobic residues by charged residues. Patients 17764 and 19964 are from the same family. In patient OV24 nucleotide 2575 is deleted and in patients 17764 and 19964 nucleotides 2993–2996 are deleted.

TABLE 12

Predisposing Mutations

Patient	Codon	Nucleotide Change	Amino Acid Change	Age of Onset	Family History
BT098	1541	$\underline{G}AG \rightarrow \underline{T}AG$	Glu → Stop	39	
OV24	819	1 bp deletion	frameshift	44	
BT106	1708	$G\underline{C}G \rightarrow G\underline{A}G$	Ala → Glu	24	+
MC44	1775	$A\underline{T}G \rightarrow A\underline{G}G$	Met → Arg	42	+
17764	958	4 bp deletion	frameshift	31	+
19964	958	4 bp deletion	frameshift		+*

*Unaffected haplotype carrier, male

Several lines of evidence suggest that all five mutations represent BRCA1 susceptibility alleles:

(i) all mutations are present in the germline;

(ii) all are absent in appropriate control populations, suggesting they are not common polymorphisms;

(iii) each mutant allele is retained in the tumor, as is the case in tumors from patients belonging to kindreds that segregate BRCA1 susceptibility alleles (Smith et al., 1992; Kelsell et al., 1993) (if the mutations represented neutral polymorphisms, they should be retained in only 50% of the cases);

(iv) the age of onset in the four breast cancer cases with mutations varied between 24 and 42 years of age, consistent with the early age of onset of breast cancer in individuals with BRCA1 susceptibility; similarly, the ovarian cancer case was diagnosed at 44, an age that falls in the youngest 13% of all ovarian cancer cases; and finally,

(v) three of the five cases have positive family histories of breast or ovarian cancer found retrospectively in their medical records, although the tumor set was not selected with regard to this criterion.

BT106 was diagnosed at a very early age with breast cancer. Her mother had ovarian cancer, her father had melanoma, and her paternal grandmother also had breast cancer. Patient MC44, an African-American, had bilateral breast cancer at an early age. This patient had a sister who died of breast cancer at a very early age. Her mutation (Met1775Arg) had been detected previously in Kindred 2099, an African-American family that segregates a BRCA1 susceptibility allele, and was absent in African-American and Caucasian controls.

Patient MC44, to our knowledge, is unrelated to Kindred 2099. The detection of a rare mutant allele, once in a BRCA1 kindred and once in the germline of an apparently unrelated early-onset breast cancer case, suggests that the Met1775Arg change may be a common predisposing mutation in African-Americans. Collectively, these observations indicate that all four BRCA1 mutations in tumors represent susceptibility alleles; no somatic mutations were detected in the samples analyzed.

The paucity of somatic BRCA1 mutations is unexpected, given the frequency of LOH on 17q, and the usual role of susceptibility genes as tumor suppressors in cancer progression. There are three possible explanations for this result: (i) some BRCA1 mutations in coding sequences were missed by our screening procedure; (ii) BRCA1 somatic mutations fall primarily outside the coding exons; and (iii) LOH events in 17q do not reflect BRCA1 somatic mutations.

If somatic BRCA1 mutations truly are rare in breast and ovary carcinomas, this would have strong implications for the biology of BRCA1. The apparent lack of somatic BRCA1 mutations implies that there may be some fundamental difference in the genesis of tumors in genetically predisposed BRCA1 carriers, compared with tumors in the general population. For example, mutations in BRCA1 may have an effect only on tumor formation at a specific stage early in breast and ovarian development. This possibility is consistent with a primary function for BRCA1 in premenopausal breast cancer. Such a model for the role of BRCA1 in breast and ovarian cancer predicts an interaction between reproductive hormones and BRCA1 function. However, no clinical or pathological differences in familial versus sporadic breast and ovary tumors, other than age of onset, have been described (Lynch et al., 1990). On the other hand, the recent finding of increased TP53 mutation and microsatellite instability in breast tumors from patients with a family history of breast cancer (Glebov et al., 1994) may reflect some difference in tumors that arise in genetically predisposed persons. The involvement of BRCA1 in this phenomenon can now be addressed directly. Alternatively, the lack of somatic BRCA1 mutations may result from the existence of multiple genes that function in the same pathway of tumor suppression as BRCA1, but which collectively represent a more favored target for mutation in sporadic tumors. Since mutation of a single element in a genetic pathway is generally sufficient to disrupt the pathway, BRCA1 might mutate at a rate that is far lower than the sum of the mutational rates of the other elements.

EXAMPLE 10

Analysis of the BRCA1 Gene

The structure and function of BRCA1 gene are determined according to the following methods.

Biological Studies. Mammalian expression vectors containing BRCA1 cDNA are constructed and transfected into appropriate breast carcinoma cells with lesions in the gene. Wild-type BRCA1 cDNA as well as altered BRCA1 cDNA are utilized. The altered BRCA1 cDNA can be obtained from altered BRCA1 alleles or produced as described below. Phenotypic reversion in cultures (e.g., cell morphology, doubling time, anchorage-independent growth) and in animals (e.g., tumorigenicity) is examined. The studies will employ both wild-type and mutant forms (Section B) of the gene.

Molecular Genetics Studies. In vitro mutagenesis is performed to construct deletion mutants and missense mutants (by single base-pair substitutions in individual codons and cluster charged→alanine scanning mutagenesis). The mutants are used in biological, biochemical and biophysical studies.

Mechanism Studies. The ability of BRCA1 protein to bind to known and unknown DNA sequences is examined. Its ability to transactivate promoters is analyzed by transient reporter expression systems in mammalian cells. Conventional procedures such as particle-capture and yeast two-hybrid system are used to discover and identify any functional partners. The nature and functions of the partners are characterized. These partners in turn are targets for drug discovery.

Structural Studies. Recombinant proteins are produced in *E. coli*, yeast, insect and/or mammalian cells and are used in crystallographical and NMR studies. Molecular modeling of the proteins is also employed. These studies facilitate structure-driven drug design.

EXAMPLE 11

Two Step Assay to Detect the Presence of BRCA1 in a Sample

Patient sample is processed according to the method disclosed by Antonarakis et al. (1985), separated through a 1% agarose gel and transferred to nylon membrane for Southern blot analysis.

Membranes are UV cross linked at 150 mJ using a GS Gene Linker (Bio-Rad). BRCA1 probe corresponding to nucleotide positions 3631–3930 of SEQ ID NO:1 is subcloned into pTZ18U. The phagemids are transformed into *E. coli* MV1190 infected with M13KO7 helper phage (Bio-Rad, Richmond, Calif.). Single stranded DNA is isolated according to standard procedures (see Sambrook et al., 1989).

Blots are prehybridized for 15–30 min at 65° C. in 7% sodium dodecyl sulfate (SDS) in 0.5M NaPO$_4$. The methods follow those described by Nguyen et al., 1992. The blots are hybridized overnight at 65° C. in 7% SDS, 0.5M NaPO$_4$ with 25–50 ng/ml single stranded probe DNA. Post-hybridization washes consist of two 30 min washes in 5% SDS, 40 mM NaPO$_4$ at 65° C., followed by two 30 min washes in 1% SDS, 40 mM NaPO$_4$ at 65° C.

Next the blots are rinsed with phosphate buffered saline (pH 6.8) for 5 min at room temperature and incubated with 0.2% casein in PBS for 30–60 min at room temperature and rinsed in PBS for 5 min. The blots are then preincubated for 5–10 minutes in a shaking water bath at 45° C. with hybridization buffer consisting of 6M urea, 0.3M NaCl, and 5X Denhardt's solution (see Sambrook, et al., 1989). The buffer is removed and replaced with 50–75 μl/cm^2 fresh hybridization buffer plus 2.5 nM of the covalently cross-linked oligonucleotide-alkaline phosphatase conjugate with the nucleotide sequence complementary to the universal primer site (UP-AP, Bio-Rad). The blots are hybridized for 20–30 min at 45° C. and post hybridization washes are incubated at 45° C. as two 10 min washes in 6M urea, 1× standard saline citrate (SSC), 0.1% SDS and one 10 min wash in 1× SSC, 0.1% Triton®X-100. The blots are rinsed for 10 min at room temperature with 1× SSC.

Blots are incubated for 10 min at room temperature with shaking in the substrate buffer consisting of 0.1M diethanolamine, 1 mM MgCl$_2$, 0.02% sodium azide, pH 10.0. Individual blots are placed in heat sealable bags with substrate buffer and 0.2 mM AMPPD (3-(2'-spiroadamantane)-4-methoxy -4-(3'-phosphoryloxy)phenyl-1,2-dioxetane, disodium salt, Bio-Rad). After a 20 min incubation at room temperature with shaking, the excess AMPPD solution is removed. The blot is exposed to X-ray film overnight. Positive bands indicate the presence of BRCA1.

EXAMPLE 12

Generation of Polyclonal Antibody against BRCA1

Segments of BRCA1 coding sequence were expressed as fusion protein in *E. coli*. The overexpressed protein was purified by gel elution and used to immunize rabbits and mice using a procedure similar to the one described by Harlow and Lane, 1988. This procedure has been shown to generate Abs against various other proteins (for example, see Kraemer et al., 1993).

Briefly, a stretch of BRCA1 coding sequence was cloned as a fusion protein in plasmid PET5A (Novagen, Inc., Madison, Wis.). The BRCA1 incorporated sequence includes the amino acids corresponding to #1361–1554 of SEQ ID NO:2. After induction with IPTG, the overexpression of a fusion protein with the expected molecular weight was verified by SDS/PAGE. Fusion protein was purified from the gel by electroelution. The identification of the protein as the BRCA1 fusion product was verified by protein sequencing at the N-terminus. Next, the purified protein was used as immunogen in rabbits. Rabbits were immunized with 100 μg of the protein in complete Freund's adjuvant and boosted twice in 3 week intervals, first with 100μg of immunogen in incomplete Freund's adjuvant followed by 100 μg of immunogen in PBS. Antibody containing serum is collected two weeks thereafter.

This procedure is repeated to generate antibodies against the mutant forms of the BRCA1 gene.

These antibodies, in conjuction with antibodies to wild type BRCA1, are used to detect the presence and the relative level of the mutant forms in various tissues and biological fluids. EXAMPILE 13

Generation of Monoclonal Antibodies Specific for BRCA1

Monoclonal antibodies are generated according to the following protocol. Mice are immunized with immunogen comprising intact BRCA1 or BRCA1 peptides (wild type or mutant) conjugated to keyhole limpet hemocyanin using glutaraldehyde or EDC as is well known.

The immunogen is mixed with an adjuvant. Each mouse receives four injections of 10 to 100 μg of immunogen and after the fourth injection blood samples are taken from the mice to determine if the serum contains antibody to the immunogen. Serum titer is determined by ELISA or RIA. Mice with sera indicating the presence of antibody to the immunogen are selected for hybridoma production.

Spleens are removed from immune mice and a single cell suspension is prepared (see Harlow and Lane, 1988). Cell fuisions are performed essentially as described by Kohler and Milstein, 1975. Briefly, P3.65.3 myeloma cells (American Type Culture Collection, Rockville, Md.) are fused with immune spleen cells using polyethylene glycol as described by Harlow and Lane, 1988. Cells are plated at a density of 2×10^5 cells/well in 96 well tissue culture plates. Individual wells are examined for growth and the supernatants of wells with growth are tested for the presence of BRCA1 specific antibodies by ELISA or RIA using wild type or mutant BRCA1 target protein. Cells in positive wells are expanded and subcloned to establish and confirm monoclonality.

Clones with the desired specificities are expanded and grown as ascites in mice or in a hollow fiber system to produce sufficient quantities of antibody for characterization and assay development.

EXAMPLE 14

Sandwich Assay for BRCA1

Monoclonal antibody is attached to a solid surface such as a plate, tube, bead, or particle. Preferably, the antibody is attached to the well surface of a 96-well ELISA plate. 100 µl sample (e.g., serum, urine, tissue cytosol) containing the BRCA1 peptide/protein (wild-type or mutant) is added to the solid phase antibody. The sample is incubated for 2 hrs at room temperature. Next the sample fluid is decanted, and the solid phase is washed with buffer to remove tunbound material. 100 µl of a second monoclonal antibody (to a different determinant on the BRCA1 peptide/protein) is added to the solid phase. This antibody is labeled with a detector molecule (e.g., ^{125}I, enzyme, fluorophore, or a chromophore) and the solid phase with the second antibody is incubated for two hrs at room temperature. The second antibody is decanted and the solid phase is washed with buffer to remove unbound material.

The amount of bound label, which is proportional to the amount of BRCA1 peptide/protein present in the sample, is quantitated. Separate assays are performed using monoclonal antibodies which are specific for the wild-type BRCA1 as well as monoclonal antibodies specific for each of the mutations identified in BRCA1.

Industrial Utility

As previously described above, the present invention provides materials and methods for use in testing BRCA1 alleles of an individual and an interpretation of the normal or predisposing nature of the alleles. Individuals at higher than normal risk might modify their lifestyles appropriately. In the case of BRCA1, the most significant non-genetic risk factor is the protective effect of an early, full term pregnancy. Therefore, women at risk could consider early childbearing or a therapy designed to simulate the hormonal effects of an early full-term pregnancy. Women at high risk would also strive for early detection and would be more highly motivated to learn and practice breast self examination. Such women would also be highly motivated to have regular mammograms, perhaps starting at an earlier age than the general population. Ovarian screening could also be undertaken at greater frequency. Diagnostic methods based on sequence analysis of the BRCA1 locus could also be applied to tumor detection and classification. Sequence analysis could be used to diagnose precursor lesions. With the evolution of the method and the accumulation of information about BRCA1 and other causative loci, it could become possible to separate cancers into benign and malignant.

Women with breast cancers may follow different surgical procedures if they are predisposed, and therefore likely to have additional cancers, than if they are not predisposed. Other therapies may be developed, using either peptides or small molecules (rational drug design). Peptides could be the missing gene product itself or a portion of the missing gene product. Alternatively, the therapeutic agent could be another molecule that mimics the deleterious gene's function, either a peptide or a nonpeptidic molecule that seeks to counteract the deleterious effect of the inherited locus. The therapy could also be gene based, through introduction of a normal BRCA1 allele into individuals to make a protein which will counteract the effect of the deleterious allele. These gene therapies may take many forms and may be directed either toward preventing the tumor from forming, curing a cancer once it has occurred, or stopping a cancer from metastasizing.

It will be appreciated that the methods and compositions of the instant invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent to the artisan that other embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

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List of Patents and Patent Applications :

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U.S. Pat. No. 5,252,479

EPO Publication No. 225,807

European Patent Application Publication No. 0332435

Geysen, H., PCT published application WO 84/03564, published 13 Sep. 1984

Hitzeman et al., EP 73,675A

PCT published application WO 93/07282

SEQUENCE LISTING

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( 1 ) GENERAL INFORMATION:

      ( i i i ) NUMBER OF SEQUENCES: 85


( 2 ) INFORMATION FOR SEQ ID NO:1:

        ( i ) SEQUENCE CHARACTERISTICS:
                ( A ) LENGTH: 5914 base pairs
                ( B ) TYPE: nucleic acid
                ( C ) STRANDEDNESS: double
                ( D ) TOPOLOGY: linear

      ( i i ) MOLECULE TYPE: cDNA

    ( i i i ) HYPOTHETICAL: NO

      ( i v ) ANTI-SENSE: NO

      ( v i ) ORIGINAL SOURCE:
                ( A ) ORGANISM: Homo sapiens

      ( i x ) FEATURE:
                ( A ) NAME/KEY: CDS
                ( B ) LOCATION: 120..5708

      ( x i ) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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ATG GAT TTA TCT GCT CTT CGC GTT GAA GAA GTA CAA AAT GTC ATT AAT       167
Met Asp Leu Ser Ala Leu Arg Val Glu Glu Val Gln Asn Val Ile Asn
1               5                   10                  15

GCT ATG CAG AAA ATC TTA GAG TGT CCC ATC TGT CTG GAG TTG ATC AAG       215
Ala Met Gln Lys Ile Leu Glu Cys Pro Ile Cys Leu Glu Leu Ile Lys
            20                  25                  30

GAA CCT GTC TCC ACA AAG TGT GAC CAC ATA TTT TGC AAA TTT TGC ATG       263
Glu Pro Val Ser Thr Lys Cys Asp His Ile Phe Cys Lys Phe Cys Met
        35                  40                  45

CTG AAA CTT CTC AAC CAG AAG AAA GGG CCT TCA CAG TGT CCT TTA TGT       311
Leu Lys Leu Leu Asn Gln Lys Lys Gly Pro Ser Gln Cys Pro Leu Cys
    50                  55                  60

AAG AAT GAT ATA ACC AAA AGG AGC CTA CAA GAA AGT ACG AGA TTT AGT       359
Lys Asn Asp Ile Thr Lys Arg Ser Leu Gln Glu Ser Thr Arg Phe Ser
65                  70                  75                  80

CAA CTT GTT GAA GAG CTA TTG AAA ATC ATT TGT GCT TTT CAG CTT GAC       407
Gln Leu Val Glu Glu Leu Leu Lys Ile Ile Cys Ala Phe Gln Leu Asp
                85                  90                  95

ACA GGT TTG GAG TAT GCA AAC AGC TAT AAT TTT GCA AAA AAG GAA AAT       455
Thr Gly Leu Glu Tyr Ala Asn Ser Tyr Asn Phe Ala Lys Lys Glu Asn
            100                 105                 110

AAC TCT CCT GAA CAT CTA AAA GAT GAA GTT TCT ATC ATC CAA AGT ATG       503
Asn Ser Pro Glu His Leu Lys Asp Glu Val Ser Ile Ile Gln Ser Met
        115                 120                 125

GGC TAC AGA AAC CGT GCC AAA AGA CTT CTA CAG AGT GAA CCC GAA AAT       551
Gly Tyr Arg Asn Arg Ala Lys Arg Leu Leu Gln Ser Glu Pro Glu Asn
    130                 135                 140

CCT TCC TTG CAG GAA ACC AGT CTC AGT GTC CAA CTC TCT AAC CTT GGA       599
Pro Ser Leu Gln Glu Thr Ser Leu Ser Val Gln Leu Ser Asn Leu Gly
145                 150                 155                 160

ACT GTG AGA ACT CTG AGG ACA AAG CAG CGG ATA CAA CCT CAA AAG ACG       647
Thr Val Arg Thr Leu Arg Thr Lys Gln Arg Ile Gln Pro Gln Lys Thr
                165                 170                 175

TCT GTC TAC ATT GAA TTG GGA TCT GAT TCT TCT GAA GAT ACC GTT AAT       695
Ser Val Tyr Ile Glu Leu Gly Ser Asp Ser Ser Glu Asp Thr Val Asn
            180                 185                 190

AAG GCA ACT TAT TGC AGT GTG GGA GAT CAA GAA TTG TTA CAA ATC ACC       743
Lys Ala Thr Tyr Cys Ser Val Gly Asp Gln Glu Leu Leu Gln Ile Thr
        195                 200                 205

CCT CAA GGA ACC AGG GAT GAA ATC AGT TTG GAT TCT GCA AAA AAG GCT       791
Pro Gln Gly Thr Arg Asp Glu Ile Ser Leu Asp Ser Ala Lys Lys Ala
    210                 215                 220

GCT TGT GAA TTT TCT GAG ACG GAT GTA ACA AAT ACT GAA CAT CAT CAA       839
Ala Cys Glu Phe Ser Glu Thr Asp Val Thr Asn Thr Glu His His Gln
225                 230                 235                 240

CCC AGT AAT AAT GAT TTG AAC ACC ACT GAG AAG CGT GCA GCT GAG AGG       887
Pro Ser Asn Asn Asp Leu Asn Thr Thr Glu Lys Arg Ala Ala Glu Arg
                245                 250                 255

CAT CCA GAA AAG TAT CAG GGT AGT TCT GTT TCA AAC TTG CAT GTG GAG       935
His Pro Glu Lys Tyr Gln Gly Ser Ser Val Ser Asn Leu His Val Glu
            260                 265                 270

CCA TGT GGC ACA AAT ACT CAT GCC AGC TCA TTA CAG CAT GAG AAC AGC       983
Pro Cys Gly Thr Asn Thr His Ala Ser Ser Leu Gln His Glu Asn Ser
        275                 280                 285

AGT TTA TTA CTC ACT AAA GAC AGA ATG AAT GTA GAA AAG GCT GAA TTC      1031
Ser Leu Leu Leu Thr Lys Asp Arg Met Asn Val Glu Lys Ala Glu Phe
    290                 295                 300

TGT AAT AAA AGC AAA CAG CCT GGC TTA GCA AGG AGC CAA CAT AAC AGA      1079
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Cys Asn Lys Ser Lys Gln Pro Gly Leu Ala Arg Ser Gln His Asn Arg
305                 310                 315                 320

TGG GCT GGA AGT AAG GAA ACA TGT AAT GAT AGG CGG ACT CCC AGC ACA       1127
Trp Ala Gly Ser Lys Glu Thr Cys Asn Asp Arg Arg Thr Pro Ser Thr
                325                 330                 335

GAA AAA AAG GTA GAT CTG AAT GCT GAT CCC CTG TGT GAG AGA AAA GAA       1175
Glu Lys Lys Val Asp Leu Asn Ala Asp Pro Leu Cys Glu Arg Lys Glu
            340                 345                 350

TGG AAT AAG CAG AAA CTG CCA TGC TCA GAG AAT CCT AGA GAT ACT GAA       1223
Trp Asn Lys Gln Lys Leu Pro Cys Ser Glu Asn Pro Arg Asp Thr Glu
        355                 360                 365

GAT GTT CCT TGG ATA ACA CTA AAT AGC AGC ATT CAG AAA GTT AAT GAG       1271
Asp Val Pro Trp Ile Thr Leu Asn Ser Ser Ile Gln Lys Val Asn Glu
    370                 375                 380

TGG TTT TCC AGA AGT GAT GAA CTG TTA GGT TCT GAT GAC TCA CAT GAT       1319
Trp Phe Ser Arg Ser Asp Glu Leu Leu Gly Ser Asp Asp Ser His Asp
385                 390                 395                 400

GGG GAG TCT GAA TCA AAT GCC AAA GTA GCT GAT GTA TTG GAC GTT CTA       1367
Gly Glu Ser Glu Ser Asn Ala Lys Val Ala Asp Val Leu Asp Val Leu
                405                 410                 415

AAT GAG GTA GAT GAA TAT TCT GGT TCT TCA GAG AAA ATA GAC TTA CTG       1415
Asn Glu Val Asp Glu Tyr Ser Gly Ser Ser Glu Lys Ile Asp Leu Leu
            420                 425                 430

GCC AGT GAT CCT CAT GAG GCT TTA ATA TGT AAA AGT GAA AGA GTT CAC       1463
Ala Ser Asp Pro His Glu Ala Leu Ile Cys Lys Ser Glu Arg Val His
        435                 440                 445

TCC AAA TCA GTA GAG AGT AAT ATT GAA GAC AAA ATA TTT GGG AAA ACC       1511
Ser Lys Ser Val Glu Ser Asn Ile Glu Asp Lys Ile Phe Gly Lys Thr
    450                 455                 460

TAT CGG AAG AAG GCA AGC CTC CCC AAC TTA AGC CAT GTA ACT GAA AAT       1559
Tyr Arg Lys Lys Ala Ser Leu Pro Asn Leu Ser His Val Thr Glu Asn
465                 470                 475                 480

CTA ATT ATA GGA GCA TTT GTT ACT GAG CCA CAG ATA ATA CAA GAG CGT       1607
Leu Ile Ile Gly Ala Phe Val Thr Glu Pro Gln Ile Ile Gln Glu Arg
                485                 490                 495

CCC CTC ACA AAT AAA TTA AAG CGT AAA AGG AGA CCT ACA TCA GGC CTT       1655
Pro Leu Thr Asn Lys Leu Lys Arg Lys Arg Arg Pro Thr Ser Gly Leu
            500                 505                 510

CAT CCT GAG GAT TTT ATC AAG AAA GCA GAT TTG GCA GTT CAA AAG ACT       1703
His Pro Glu Asp Phe Ile Lys Lys Ala Asp Leu Ala Val Gln Lys Thr
        515                 520                 525

CCT GAA ATG ATA AAT CAG GGA ACT AAC CAA ACG GAG CAG AAT GGT CAA       1751
Pro Glu Met Ile Asn Gln Gly Thr Asn Gln Thr Glu Gln Asn Gly Gln
    530                 535                 540

GTG ATG AAT ATT ACT AAT AGT GGT CAT GAG AAT AAA ACA AAA GGT GAT       1799
Val Met Asn Ile Thr Asn Ser Gly His Glu Asn Lys Thr Lys Gly Asp
545                 550                 555                 560

TCT ATT CAG AAT GAG AAA AAT CCT AAC CCA ATA GAA TCA CTC GAA AAA       1847
Ser Ile Gln Asn Glu Lys Asn Pro Asn Pro Ile Glu Ser Leu Glu Lys
                565                 570                 575

GAA TCT GCT TTC AAA ACG AAA GCT GAA CCT ATA AGC AGC AGT ATA AGC       1895
Glu Ser Ala Phe Lys Thr Lys Ala Glu Pro Ile Ser Ser Ser Ile Ser
            580                 585                 590

AAT ATG GAA CTC GAA TTA AAT ATC CAC AAT TCA AAA GCA CCT AAA AAG       1943
Asn Met Glu Leu Glu Leu Asn Ile His Asn Ser Lys Ala Pro Lys Lys
        595                 600                 605

AAT AGG CTG AGG AGG AAG TCT TCT ACC AGG CAT ATT CAT GCG CTT GAA       1991
Asn Arg Leu Arg Arg Lys Ser Ser Thr Arg His Ile His Ala Leu Glu
    610                 615                 620

CTA GTA GTC AGT AGA AAT CTA AGC CCA CCT AAT TGT ACT GAA TTG CAA       2039
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Leu Val Val Ser Arg Asn Leu Ser Pro Pro Asn Cys Thr Gln Leu Gln
625                 630                 635                 640

ATT GAT AGT TGT TCT AGC AGT GAA GAG ATA AAG AAA AAA AAG TAC AAC        2087
Ile Asp Ser Cys Ser Ser Ser Glu Glu Ile Lys Lys Lys Lys Tyr Asn
                645                 650                 655

CAA ATG CCA GTC AGG CAC AGC AGA AAC CTA CAA CTC ATG GAA GGT AAA        2135
Gln Met Pro Val Arg His Ser Arg Asn Leu Gln Leu Met Glu Gly Lys
            660                 665                 670

GAA CCT GCA ACT GGA GCC AAG AAG AGT AAC AAG CCA AAT GAA CAG ACA        2183
Glu Pro Ala Thr Gly Ala Lys Lys Ser Asn Lys Pro Asn Glu Gln Thr
        675                 680                 685

AGT AAA AGA CAT GAC AGC GAT ACT TTC CCA GAG CTG AAG TTA ACA AAT        2231
Ser Lys Arg His Asp Ser Asp Thr Phe Pro Glu Leu Lys Leu Thr Asn
    690                 695                 700

GCA CCT GGT TCT TTT ACT AAG TGT TCA AAT ACC AGT GAA CTT AAA GAA        2279
Ala Pro Gly Ser Phe Thr Lys Cys Ser Asn Thr Ser Glu Leu Lys Glu
705                 710                 715                 720

TTT GTC AAT CCT AGC CTT CCA AGA GAA GAA AAA GAA GAG AAA CTA GAA        2327
Phe Val Asn Pro Ser Leu Pro Arg Glu Glu Lys Glu Glu Lys Leu Glu
                725                 730                 735

ACA GTT AAA GTG TCT AAT AAT GCT GAA GAC CCC AAA GAT CTC ATG TTA        2375
Thr Val Lys Val Ser Asn Asn Ala Glu Asp Pro Lys Asp Leu Met Leu
            740                 745                 750

AGT GGA GAA AGG GTT TTG CAA ACT GAA AGA TCT GTA GAG AGT AGC AGT        2423
Ser Gly Glu Arg Val Leu Gln Thr Glu Arg Ser Val Glu Ser Ser Ser
        755                 760                 765

ATT TCA TTG GTA CCT GGT ACT GAT TAT GGC ACT CAG GAA AGT ATC TCG        2471
Ile Ser Leu Val Pro Gly Thr Asp Tyr Gly Thr Gln Glu Ser Ile Ser
    770                 775                 780

TTA CTG GAA GTT AGC ACT CTA GGG AAG GCA AAA ACA GAA CCA AAT AAA        2519
Leu Leu Glu Val Ser Thr Leu Gly Lys Ala Lys Thr Glu Pro Asn Lys
785                 790                 795                 800

TGT GTG AGT CAG TGT GCA GCA TTT GAA AAC CCC AAG GGA CTA ATT CAT        2567
Cys Val Ser Gln Cys Ala Ala Phe Glu Asn Pro Lys Gly Leu Ile His
                805                 810                 815

GGT TGT TCC AAA GAT AAT AGA AAT GAC ACA GAA GGC TTT AAG TAT CCA        2615
Gly Cys Ser Lys Asp Asn Arg Asn Asp Thr Glu Gly Phe Lys Tyr Pro
            820                 825                 830

TTG GGA CAT GAA GTT AAC CAC AGT CGG GAA ACA AGC ATA GAA ATG GAA        2663
Leu Gly His Glu Val Asn His Ser Arg Glu Thr Ser Ile Glu Met Glu
        835                 840                 845

GAA AGT GAA CTT GAT GCT CAG TAT TTG CAG AAT ACA TTC AAG GTT TCA        2711
Glu Ser Glu Leu Asp Ala Gln Tyr Leu Gln Asn Thr Phe Lys Val Ser
    850                 855                 860

AAG CGC CAG TCA TTT GCT CCG TTT TCA AAT CCA GGA AAT GCA GAA GAG        2759
Lys Arg Gln Ser Phe Ala Pro Phe Ser Asn Pro Gly Asn Ala Glu Glu
865                 870                 875                 880

GAA TGT GCA ACA TTC TCT GCC CAC TCT GGG TCC TTA AAG AAA CAA AGT        2807
Glu Cys Ala Thr Phe Ser Ala His Ser Gly Ser Leu Lys Lys Gln Ser
                885                 890                 895

CCA AAA GTC ACT TTT GAA TGT GAA CAA AAG GAA GAA AAT CAA GGA AAG        2855
Pro Lys Val Thr Phe Glu Cys Glu Gln Lys Glu Glu Asn Gln Gly Lys
            900                 905                 910

AAT GAG TCT AAT ATC AAG CCT GTA CAG ACA GTT AAT ATC ACT GCA GGC        2903
Asn Glu Ser Asn Ile Lys Pro Val Gln Thr Val Asn Ile Thr Ala Gly
        915                 920                 925

TTT CCT GTG GTT GGT CAG AAA GAT AAG CCA GTT GAT AAT GCC AAA TGT        2951
Phe Pro Val Val Gly Gln Lys Asp Lys Pro Val Asp Asn Ala Lys Cys
    930                 935                 940

AGT ATC AAA GGA GGC TCT AGG TTT TGT CTA TCA TCT CAG TTC AGA GGC        2999
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Ser Ile Lys Gly Gly Ser Arg Phe Cys Leu Ser Ser Gln Phe Arg Gly
945                 950                 955                 960

AAC GAA ACT GGA CTC ATT ACT CCA AAT AAA CAT GGA CTT TTA CAA AAC      3047
Asn Glu Thr Gly Leu Ile Thr Pro Asn Lys His Gly Leu Leu Gln Asn
                965                 970                 975

CCA TAT CGT ATA CCA CCA CTT TTT CCC ATC AAG TCA TTT GTT AAA ACT      3095
Pro Tyr Arg Ile Pro Pro Leu Phe Pro Ile Lys Ser Phe Val Lys Thr
            980                 985                 990

AAA TGT AAG AAA AAT CTG CTA GAG GAA AAC TTT GAG GAA CAT TCA ATG      3143
Lys Cys Lys Lys Asn Leu Leu Glu Glu Asn Phe Glu Glu His Ser Met
        995                 1000                1005

TCA CCT GAA AGA GAA ATG GGA AAT GAG AAC ATT CCA AGT ACA GTG AGC      3191
Ser Pro Glu Arg Glu Met Gly Asn Glu Asn Ile Pro Ser Thr Val Ser
    1010                1015                1020

ACA ATT AGC CGT AAT AAC ATT AGA GAA AAT GTT TTT AAA GAA GCC AGC      3239
Thr Ile Ser Arg Asn Asn Ile Arg Glu Asn Val Phe Lys Glu Ala Ser
1025                1030                1035                1040

TCA AGC AAT ATT AAT GAA GTA GGT TCC AGT ACT AAT GAA GTG GGC TCC      3287
Ser Ser Asn Ile Asn Glu Val Gly Ser Ser Thr Asn Glu Val Gly Ser
                1045                1050                1055

AGT ATT AAT GAA ATA GGT TCC AGT GAT GAA AAC ATT CAA GCA GAA CTA      3335
Ser Ile Asn Glu Ile Gly Ser Ser Asp Glu Asn Ile Gln Ala Glu Leu
            1060                1065                1070

GGT AGA AAC AGA GGG CCA AAA TTG AAT GCT ATG CTT AGA TTA GGG GTT      3383
Gly Arg Asn Arg Gly Pro Lys Leu Asn Ala Met Leu Arg Leu Gly Val
        1075                1080                1085

TTG CAA CCT GAG GTC TAT AAA CAA AGT CTT CCT GGA AGT AAT TGT AAG      3431
Leu Gln Pro Glu Val Tyr Lys Gln Ser Leu Pro Gly Ser Asn Cys Lys
    1090                1095                1100

CAT CCT GAA ATA AAA AAG CAA GAA TAT GAA GAA GTA GTT CAG ACT GTT      3479
His Pro Glu Ile Lys Lys Gln Glu Tyr Glu Glu Val Val Gln Thr Val
1105                1110                1115                1120

AAT ACA GAT TTC TCT CCA TAT CTG ATT TCA GAT AAC TTA GAA CAG CCT      3527
Asn Thr Asp Phe Ser Pro Tyr Leu Ile Ser Asp Asn Leu Glu Gln Pro
                1125                1130                1135

ATG GGA AGT AGT CAT GCA TCT CAG GTT TGT TCT GAG ACA CCT GAT GAC      3575
Met Gly Ser Ser His Ala Ser Gln Val Cys Ser Glu Thr Pro Asp Asp
            1140                1145                1150

CTG TTA GAT GAT GGT GAA ATA AAG GAA GAT ACT AGT TTT GCT GAA AAT      3623
Leu Leu Asp Asp Gly Glu Ile Lys Glu Asp Thr Ser Phe Ala Glu Asn
        1155                1160                1165

GAC ATT AAG GAA AGT TCT GCT GTT TTT AGC AAA AGC GTC CAG AAA GGA      3671
Asp Ile Lys Glu Ser Ser Ala Val Phe Ser Lys Ser Val Gln Lys Gly
    1170                1175                1180

GAG CTT AGC AGG AGT CCT AGC CCT TTC ACC CAT ACA CAT TTG GCT CAG      3719
Glu Leu Ser Arg Ser Pro Ser Pro Phe Thr His Thr His Leu Ala Gln
1185                1190                1195                1200

GGT TAC CGA AGA GGG GCC AAG AAA TTA GAG TCC TCA GAA GAG AAC TTA      3767
Gly Tyr Arg Arg Gly Ala Lys Lys Leu Glu Ser Ser Glu Glu Asn Leu
                1205                1210                1215

TCT AGT GAG GAT GAA GAG CTT CCC TGC TTC CAA CAC TTG TTA TTT GGT      3815
Ser Ser Glu Asp Glu Glu Leu Pro Cys Phe Gln His Leu Leu Phe Gly
            1220                1225                1230

AAA GTA AAC AAT ATA CCT TCT CAG TCT ACT AGG CAT AGC ACC GTT GCT      3863
Lys Val Asn Asn Ile Pro Ser Gln Ser Thr Arg His Ser Thr Val Ala
        1235                1240                1245

ACC GAG TGT CTG TCT AAG AAC ACA GAG GAG AAT TTA TTA TCA TTG AAG      3911
Thr Glu Cys Leu Ser Lys Asn Thr Glu Glu Asn Leu Leu Ser Leu Lys
    1250                1255                1260

AAT AGC TTA AAT GAC TGC AGT AAC CAG GTA ATA TTG GCA AAG GCA TCT      3959
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Asn Ser Leu Asn Asp Cys Ser Asn Gln Val Ile Leu Ala Lys Ala Ser
1265                1270                1275                1280

CAG GAA CAT CAC CTT AGT GAG GAA ACA AAA TGT TCT GCT AGC TTG TTT         4007
Gln Glu His His Leu Ser Glu Glu Thr Lys Cys Ser Ala Ser Leu Phe
                1285                1290                1295

TCT TCA CAG TGC AGT GAA TTG GAA GAC TTG ACT GCA AAT ACA AAC ACC         4055
Ser Ser Gln Cys Ser Glu Leu Glu Asp Leu Thr Ala Asn Thr Asn Thr
            1300                1305                1310

CAG GAT CCT TTC TTG ATT GGT TCT TCC AAA CAA ATG AGG CAT CAG TCT         4103
Gln Asp Pro Phe Leu Ile Gly Ser Ser Lys Gln Met Arg His Gln Ser
        1315                1320                1325

GAA AGC CAG GGA GTT GGT CTG AGT GAC AAG GAA TTG GTT TCA GAT GAT         4151
Glu Ser Gln Gly Val Gly Leu Ser Asp Lys Glu Leu Val Ser Asp Asp
    1330                1335                1340

GAA GAA AGA GGA ACG GGC TTG GAA GAA AAT AAT CAA GAA GAG CAA AGC         4199
Glu Glu Arg Gly Thr Gly Leu Glu Glu Asn Asn Gln Glu Glu Gln Ser
1345                1350                1355                1360

ATG GAT TCA AAC TTA GGT GAA GCA GCA TCT GGG TGT GAG AGT GAA ACA         4247
Met Asp Ser Asn Leu Gly Glu Ala Ala Ser Gly Cys Glu Ser Glu Thr
                1365                1370                1375

AGC GTC TCT GAA GAC TGC TCA GGG CTA TCC TCT CAG AGT GAC ATT TTA         4295
Ser Val Ser Glu Asp Cys Ser Gly Leu Ser Ser Gln Ser Asp Ile Leu
            1380                1385                1390

ACC ACT CAG CAG AGG GAT ACC ATG CAA CAT AAC CTG ATA AAG CTC CAG         4343
Thr Thr Gln Gln Arg Asp Thr Met Gln His Asn Leu Ile Lys Leu Gln
        1395                1400                1405

CAG GAA ATG GCT GAA CTA GAA GCT GTG TTA GAA CAG CAT GGG AGC CAG         4391
Gln Glu Met Ala Glu Leu Glu Ala Val Leu Glu Gln His Gly Ser Gln
    1410                1415                1420

CCT TCT AAC AGC TAC CCT TCC ATC ATA AGT GAC TC[illegible] GCC CTT GAG         4439
Pro Ser Asn Ser Tyr Pro Ser Ile Ile Ser Asp Se[illegible] Ala Leu Glu
1425                1430                1435                1440

GAC CTG CGA AAT CCA GAA CAA AGC ACA TCA GAA AAA GCA GTA TTA ACT         4487
Asp Leu Arg Asn Pro Glu Gln Ser Thr Ser Glu Lys Ala Val Leu Thr
                1445                1450                1455

TCA CAG AAA AGT AGT GAA TAC CCT ATA AGC CAG AAT CCA GAA GGC CTT         4535
Ser Gln Lys Ser Ser Glu Tyr Pro Ile Ser Gln Asn Pro Glu Gly Leu
            1460                1465                1470

TCT GCT GAC AAG TTT GAG GTG TCT GCA GAT AGT TCT ACC AGT AAA AAT         4583
Ser Ala Asp Lys Phe Glu Val Ser Ala Asp Ser Ser Thr Ser Lys Asn
        1475                1480                1485

AAA GAA CCA GGA GTG GAA AGG TCA TCC CCT TCT AAA TGC CCA TCA TTA         4631
Lys Glu Pro Gly Val Glu Arg Ser Ser Pro Ser Lys Cys Pro Ser Leu
    1490                1495                1500

GAT GAT AGG TGG TAC ATG CAC AGT TGC TCT GGG AGT CTT CAG AAT AGA         4679
Asp Asp Arg Trp Tyr Met His Ser Cys Ser Gly Ser Leu Gln Asn Arg
1505                1510                1515                1520

AAC TAC CCA TCT CAA GAG GAG CTC ATT AAG GTT GTT GAT GTG GAG GAG         4727
Asn Tyr Pro Ser Gln Glu Glu Leu Ile Lys Val Val Asp Val Glu Glu
                1525                1530                1535

CAA CAG CTG GAA GAG TCT GGG CCA CAC GAT TTG ACG GAA ACA TCT TAC         4775
Gln Gln Leu Glu Glu Ser Gly Pro His Asp Leu Thr Glu Thr Ser Tyr
            1540                1545                1550

TTG CCA AGG CAA GAT CTA GAG GGA ACC CCT TAC CTG GAA TCT GGA ATC         4823
Leu Pro Arg Gln Asp Leu Glu Gly Thr Pro Tyr Leu Glu Ser Gly Ile
        1555                1560                1565

AGC CTC TTC TCT GAT GAC CCT GAA TCT GAT CCT TCT GAA GAC AGA GCC         4871
Ser Leu Phe Ser Asp Asp Pro Glu Ser Asp Pro Ser Glu Asp Arg Ala
    1570                1575                1580

CCA GAG TCA GCT CGT GTT GGC AAC ATA CCA TCT TCA ACC TCT GCA TTG         4919
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Pro Glu Ser Ala Arg Val Gly Asn Ile Pro Ser Ser Thr Ser Ala Leu
1585                1590                1595                1600

AAA GTT CCC CAA TTG AAA GTT GCA GAA TCT GCC CAG AGT CCA GCT GCT       4967
Lys Val Pro Gln Leu Lys Val Ala Glu Ser Ala Gln Ser Pro Ala Ala
                1605                1610                1615

GCT CAT ACT ACT GAT ACT GCT GGG TAT AAT GCA ATG GAA GAA AGT GTG       5015
Ala His Thr Thr Asp Thr Ala Gly Tyr Asn Ala Met Glu Glu Ser Val
            1620                1625                1630

AGC AGG GAG AAG CCA GAA TTG ACA GCT TCA ACA GAA AGG GTC AAC AAA       5063
Ser Arg Glu Lys Pro Glu Leu Thr Ala Ser Thr Glu Arg Val Asn Lys
        1635                1640                1645

AGA ATG TCC ATG GTG GTG TCT GGC CTG ACC CCA GAA GAA TTT ATG CTC       5111
Arg Met Ser Met Val Val Ser Gly Leu Thr Pro Glu Glu Phe Met Leu
    1650                1655                1660

GTG TAC AAG TTT GCC AGA AAA CAC CAC ATC ACT TTA ACT AAT CTA ATT       5159
Val Tyr Lys Phe Ala Arg Lys His His Ile Thr Leu Thr Asn Leu Ile
1665                1670                1675                1680

ACT GAA GAG ACT ACT CAT GTT GTT ATG AAA ACA GAT GCT GAG TTT GTG       5207
Thr Glu Glu Thr Thr His Val Val Met Lys Thr Asp Ala Glu Phe Val
                1685                1690                1695

TGT GAA CGG ACA CTG AAA TAT TTT CTA GGA ATT GCG GGA GGA AAA TGG       5255
Cys Glu Arg Thr Leu Lys Tyr Phe Leu Gly Ile Ala Gly Gly Lys Trp
            1700                1705                1710

GTA GTT AGC TAT TTC TGG GTG ACC CAG TCT ATT AAA GAA AGA AAA ATG       5303
Val Val Ser Tyr Phe Trp Val Thr Gln Ser Ile Lys Glu Arg Lys Met
        1715                1720                1725

CTG AAT GAG CAT GAT TTT GAA GTC AGA GGA GAT GTG GTC AAT GGA AGA       5351
Leu Asn Glu His Asp Phe Glu Val Arg Gly Asp Val Val Asn Gly Arg
    1730                1735                1740

AAC CAC CAA GGT CCA AAG CGA GCA AGA GAA TCC CAG GAC AGA AAG ATC       5399
Asn His Gln Gly Pro Lys Arg Ala Arg Glu Ser Gln Asp Arg Lys Ile
1745                1750                1755                1760

TTC AGG GGG CTA GAA ATC TGT TGC TAT GGG CCC TTC ACC AAC ATG CCC       5447
Phe Arg Gly Leu Glu Ile Cys Cys Tyr Gly Pro Phe Thr Asn Met Pro
                1765                1770                1775

ACA GAT CAA CTG GAA TGG ATG GTA CAG CTG TGT GGT GCT TCT GTG GTG       5495
Thr Asp Gln Leu Glu Trp Met Val Gln Leu Cys Gly Ala Ser Val Val
            1780                1785                1790

AAG GAG CTT TCA TCA TTC ACC CTT GGC ACA GGT GTC CAC CCA ATT GTG       5543
Lys Glu Leu Ser Ser Phe Thr Leu Gly Thr Gly Val His Pro Ile Val
        1795                1800                1805

GTT GTG CAG CCA GAT GCC TGG ACA GAG GAC AAT GGC TTC CAT GCA ATT       5591
Val Val Gln Pro Asp Ala Trp Thr Glu Asp Asn Gly Phe His Ala Ile
    1810                1815                1820

GGG CAG ATG TGT GAG GCA CCT GTG GTG ACC CGA GAG TGG GTG TTG GAC       5639
Gly Gln Met Cys Glu Ala Pro Val Val Thr Arg Glu Trp Val Leu Asp
1825                1830                1835                1840

AGT GTA GCA CTC TAC CAG TGC CAG GAG CTG GAC ACC TAC CTG ATA CCC       5687
Ser Val Ala Leu Tyr Gln Cys Gln Glu Leu Asp Thr Tyr Leu Ile Pro
                1845                1850                1855

CAG ATC CCC CAC AGC CAC TAC TGA CTGCAGCCAG CCACAGGTAC AGAGCCACAG      5741
Gln Ile Pro His Ser His Tyr
            1860

GACCCCAAGA ATGAGCTTAC AAAGTGGCCT TTCCAGGCCC TGGGAGCTCC TCTCACTCTT     5801

CAGTCCTTCT ACTGTCCTGG CTACTAAATA TTTTATGTAC ATCAGCCTGA AAAGGACTTC     5861

TGGCTATGCA AGGGTCCCTT AAAGATTTTC TGCTTGAAGT CTCCCTTGGA AAT            5914
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(2) INFORMATION FOR SEQ ID NO:2:

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(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1863 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: protein

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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Met Asp Leu Ser Ala Leu Arg Val Glu Glu Val Gln Asn Val Ile Asn
1               5                   10                  15

Ala Met Gln Lys Ile Leu Glu Cys Pro Ile Cys Leu Glu Leu Ile Lys
            20                  25                  30

Glu Pro Val Ser Thr Lys Cys Asp His Ile Phe Cys Lys Phe Cys Met
        35                  40                  45

Leu Lys Leu Leu Asn Gln Lys Lys Gly Pro Ser Gln Cys Pro Leu Cys
    50                  55                  60

Lys Asn Asp Ile Thr Lys Arg Ser Leu Gln Glu Ser Thr Arg Phe Ser
65                  70                  75                  80

Gln Leu Val Glu Glu Leu Leu Lys Ile Ile Cys Ala Phe Gln Leu Asp
                85                  90                  95

Thr Gly Leu Glu Tyr Ala Asn Ser Tyr Asn Phe Ala Lys Lys Glu Asn
            100                 105                 110

Asn Ser Pro Glu His Leu Lys Asp Glu Val Ser Ile Ile Gln Ser Met
        115                 120                 125

Gly Tyr Arg Asn Arg Ala Lys Arg Leu Leu Gln Ser Glu Pro Glu Asn
    130                 135                 140

Pro Ser Leu Gln Glu Thr Ser Leu Ser Val Gln Leu Ser Asn Leu Gly
145                 150                 155                 160

Thr Val Arg Thr Leu Arg Thr Lys Gln Arg Ile Gln Pro Gln Lys Thr
                165                 170                 175

Ser Val Tyr Ile Glu Leu Gly Ser Asp Ser Ser Glu Asp Thr Val Asn
            180                 185                 190

Lys Ala Thr Tyr Cys Ser Val Gly Asp Gln Glu Leu Leu Gln Ile Thr
        195                 200                 205

Pro Gln Gly Thr Arg Asp Glu Ile Ser Leu Asp Ser Ala Lys Lys Ala
    210                 215                 220

Ala Cys Glu Phe Ser Glu Thr Asp Val Thr Asn Thr Glu His His Gln
225                 230                 235                 240

Pro Ser Asn Asn Asp Leu Asn Thr Thr Glu Lys Arg Ala Ala Glu Arg
                245                 250                 255

His Pro Glu Lys Tyr Gln Gly Ser Ser Val Ser Asn Leu His Val Glu
            260                 265                 270

Pro Cys Gly Thr Asn Thr His Ala Ser Ser Leu Gln His Glu Asn Ser
        275                 280                 285

Ser Leu Leu Leu Thr Lys Asp Arg Met Asn Val Glu Lys Ala Glu Phe
    290                 295                 300

Cys Asn Lys Ser Lys Gln Pro Gly Leu Ala Arg Ser Gln His Asn Arg
305                 310                 315                 320

Trp Ala Gly Ser Lys Glu Thr Cys Asn Asp Arg Arg Thr Pro Ser Thr
                325                 330                 335

Glu Lys Lys Val Asp Leu Asn Ala Asp Pro Leu Cys Glu Arg Lys Glu
            340                 345                 350

Trp Asn Lys Gln Lys Leu Pro Cys Ser Glu Asn Pro Arg Asp Thr Glu
        355                 360                 365

Asp Val Pro Trp Ile Thr Leu Asn Ser Ser Ile Gln Lys Val Asn Glu
    370                 375                 380
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Trp Phe Ser Arg Ser Asp Glu Leu Leu Gly Ser Asp Asp Ser His Asp
385                 390                 395                 400

Gly Glu Ser Glu Ser Asn Ala Lys Val Ala Asp Val Leu Asp Val Leu
                405                 410                 415

Asn Glu Val Asp Glu Tyr Ser Gly Ser Ser Glu Lys Ile Asp Leu Leu
            420                 425                 430

Ala Ser Asp Pro His Glu Ala Leu Ile Cys Lys Ser Glu Arg Val His
        435                 440                 445

Ser Lys Ser Val Gln Ser Asn Ile Glu Asp Lys Ile Phe Gly Lys Thr
    450                 455                 460

Tyr Arg Lys Lys Ala Ser Leu Pro Asn Leu Ser His Val Thr Glu Asn
465                 470                 475                 480

Leu Ile Ile Gly Ala Phe Val Thr Glu Pro Gln Ile Ile Gln Glu Arg
                485                 490                 495

Pro Leu Thr Asn Lys Leu Lys Arg Lys Arg Arg Pro Thr Ser Gly Leu
            500                 505                 510

His Pro Gln Asp Phe Ile Lys Lys Ala Asp Leu Ala Val Gln Lys Thr
        515                 520                 525

Pro Glu Met Ile Asn Gln Gly Thr Asn Gln Thr Glu Gln Asn Gly Gln
    530                 535                 540

Val Met Asn Ile Thr Asn Ser Gly His Glu Asn Lys Thr Lys Gly Asp
545                 550                 555                 560

Ser Ile Gln Asn Glu Lys Asn Pro Asn Pro Ile Glu Ser Leu Glu Lys
                565                 570                 575

Glu Ser Ala Phe Lys Thr Lys Ala Glu Pro Ile Ser Ser Ser Ile Ser
            580                 585                 590

Asn Met Glu Leu Gln Leu Asn Ile His Asn Ser Lys Ala Pro Lys Lys
        595                 600                 605

Asn Arg Leu Arg Arg Lys Ser Ser Thr Arg His Ile His Ala Leu Gln
    610                 615                 620

Leu Val Val Ser Arg Asn Leu Ser Pro Pro Asn Cys Thr Glu Leu Gln
625                 630                 635                 640

Ile Asp Ser Cys Ser Ser Ser Glu Gln Ile Lys Lys Lys Lys Tyr Asn
                645                 650                 655

Gln Met Pro Val Arg His Ser Arg Asn Leu Gln Leu Met Gln Gly Lys
            660                 665                 670

Glu Pro Ala Thr Gly Ala Lys Lys Ser Asn Lys Pro Asn Glu Gln Thr
        675                 680                 685

Ser Lys Arg His Asp Ser Asp Thr Phe Pro Gln Leu Lys Leu Thr Asn
    690                 695                 700

Ala Pro Gly Ser Phe Thr Lys Cys Ser Asn Thr Ser Glu Leu Lys Gln
705                 710                 715                 720

Phe Val Asn Pro Ser Leu Pro Arg Glu Glu Lys Glu Glu Lys Leu Glu
                725                 730                 735

Thr Val Lys Val Ser Asn Asn Ala Glu Asp Pro Lys Asp Leu Met Leu
            740                 745                 750

Ser Gly Glu Arg Val Leu Gln Thr Gln Arg Ser Val Glu Ser Ser Ser
        755                 760                 765

Ile Ser Leu Val Pro Gly Thr Asp Tyr Gly Thr Gln Glu Ser Ile Ser
    770                 775                 780

Leu Leu Glu Val Ser Thr Leu Gly Lys Ala Lys Thr Glu Pro Asn Lys
785                 790                 795                 800

Cys Val Ser Gln Cys Ala Ala Phe Glu Asn Pro Lys Gly Leu Ile His
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                805                 810                 815

Gly Cys Ser Lys Asp Asn Arg Asn Asp Thr Gln Gly Phe Lys Tyr Pro
            820                 825                 830

Leu Gly His Glu Val Asn His Ser Arg Glu Thr Ser Ile Glu Met Gln
        835                 840                 845

Glu Ser Gln Leu Asp Ala Gln Tyr Leu Gln Asn Thr Phe Lys Val Ser
    850                 855                 860

Lys Arg Gln Ser Phe Ala Pro Phe Ser Asn Pro Gly Asn Ala Gln Gln
865                 870                 875                 880

Glu Cys Ala Thr Phe Ser Ala His Ser Gly Ser Leu Lys Lys Gln Ser
                885                 890                 895

Pro Lys Val Thr Phe Glu Cys Gln Gln Lys Gln Glu Asn Gln Gly Lys
            900                 905                 910

Asn Gln Ser Asn Ile Lys Pro Val Gln Thr Val Asn Ile Thr Ala Gly
        915                 920                 925

Phe Pro Val Val Gly Gln Lys Asp Lys Pro Val Asp Asn Ala Lys Cys
    930                 935                 940

Ser Ile Lys Gly Gly Ser Arg Phe Cys Leu Ser Ser Gln Phe Arg Gly
945                 950                 955                 960

Asn Gln Thr Gly Leu Ile Thr Pro Asn Lys His Gly Leu Leu Gln Asn
                965                 970                 975

Pro Tyr Arg Ile Pro Pro Leu Phe Pro Ile Lys Ser Phe Val Lys Thr
            980                 985                 990

Lys Cys Lys Lys Asn Leu Leu Gln Glu Asn Phe Gln Glu His Ser Met
        995                 1000                1005

Ser Pro Gln Arg Gln Met Gly Asn Gln Asn Ile Pro Ser Thr Val Ser
    1010                1015                1020

Thr Ile Ser Arg Asn Asn Ile Arg Glu Asn Val Phe Lys Glu Ala Ser
1025                1030                1035                1040

Ser Ser Asn Ile Asn Glu Val Gly Ser Ser Thr Asn Glu Val Gly Ser
                1045                1050                1055

Ser Ile Asn Glu Ile Gly Ser Ser Asp Glu Asn Ile Gln Ala Glu Leu
            1060                1065                1070

Gly Arg Asn Arg Gly Pro Lys Leu Asn Ala Met Leu Arg Leu Gly Val
        1075                1080                1085

Leu Gln Pro Gln Val Tyr Lys Gln Ser Leu Pro Gly Ser Asn Cys Lys
    1090                1095                1100

His Pro Glu Ile Lys Lys Gln Gln Tyr Glu Glu Val Val Gln Thr Val
1105                1110                1115                1120

Asn Thr Asp Phe Ser Pro Tyr Leu Ile Ser Asp Asn Leu Glu Gln Pro
                1125                1130                1135

Met Gly Ser Ser His Ala Ser Gln Val Cys Ser Glu Thr Pro Asp Asp
            1140                1145                1150

Leu Leu Asp Asp Gly Glu Ile Lys Glu Asp Thr Ser Phe Ala Glu Asn
        1155                1160                1165

Asp Ile Lys Glu Ser Ser Ala Val Phe Ser Lys Ser Val Gln Lys Gly
    1170                1175                1180

Glu Leu Ser Arg Ser Pro Ser Pro Phe Thr His Thr His Leu Ala Gln
1185                1190                1195                1200

Gly Tyr Arg Arg Gly Ala Lys Lys Leu Glu Ser Ser Glu Glu Asn Leu
                1205                1210                1215

Ser Ser Glu Asp Glu Glu Leu Pro Cys Phe Gln His Leu Leu Phe Gly
            1220                1225                1230
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Lys Val Asn Asn Ile Pro Ser Gln Ser Thr Arg His Ser Thr Val Ala
        1235                1240                1245

Thr Glu Cys Leu Ser Lys Asn Thr Gln Glu Asn Leu Leu Ser Leu Lys
    1250                1255                1260

Asn Ser Leu Asn Asp Cys Ser Asn Gln Val Ile Leu Ala Lys Ala Ser
1265                1270                1275                1280

Gln Gln His His Leu Ser Glu Glu Thr Lys Cys Ser Ala Ser Leu Phe
                1285                1290                1295

Ser Ser Gln Cys Ser Glu Leu Glu Asp Leu Thr Ala Asn Thr Asn Thr
            1300                1305                1310

Gln Asp Pro Phe Leu Ile Gly Ser Ser Lys Gln Met Arg His Gln Ser
        1315                1320                1325

Glu Ser Gln Gly Val Gly Leu Ser Asp Lys Glu Leu Val Ser Asp Asp
    1330                1335                1340

Glu Gln Arg Gly Thr Gly Leu Glu Gln Asn Asn Gln Glu Glu Gln Ser
1345                1350                1355                1360

Met Asp Ser Asn Leu Gly Glu Ala Ala Ser Gly Cys Gln Ser Glu Thr
                1365                1370                1375

Ser Val Ser Glu Asp Cys Ser Gly Leu Ser Ser Gln Ser Asp Ile Leu
            1380                1385                1390

Thr Thr Gln Gln Arg Asp Thr Met Gln His Asn Leu Ile Lys Leu Gln
        1395                1400                1405

Gln Glu Met Ala Glu Leu Glu Ala Val Leu Glu Gln His Gly Ser Gln
    1410                1415                1420

Pro Ser Asn Ser Tyr Pro Ser Ile Ile Ser Asp Ser Ser Ala Leu Glu
1425                1430                1435                1440

Asp Leu Arg Asn Pro Glu Gln Ser Thr Ser Glu Lys Ala Val Leu Thr
                1445                1450                1455

Ser Gln Lys Ser Ser Glu Tyr Pro Ile Ser Gln Asn Pro Glu Gly Leu
            1460                1465                1470

Ser Ala Asp Lys Phe Glu Val Ser Ala Asp Ser Ser Thr Ser Lys Asn
        1475                1480                1485

Lys Glu Pro Gly Val Glu Arg Ser Ser Pro Ser Lys Cys Pro Ser Leu
    1490                1495                1500

Asp Asp Arg Trp Tyr Met His Ser Cys Ser Gly Ser Leu Gln Asn Arg
1505                1510                1515                1520

Asn Tyr Pro Ser Gln Glu Glu Leu Ile Lys Val Val Asp Val Glu Glu
                1525                1530                1535

Gln Gln Leu Glu Glu Ser Gly Pro His Asp Leu Thr Glu Thr Ser Tyr
            1540                1545                1550

Leu Pro Arg Gln Asp Leu Glu Gly Thr Pro Tyr Leu Glu Ser Gly Ile
        1555                1560                1565

Ser Leu Phe Ser Asp Asp Pro Glu Ser Asp Pro Ser Glu Asp Arg Ala
    1570                1575                1580

Pro Glu Ser Ala Arg Val Gly Asn Ile Pro Ser Ser Thr Ser Ala Leu
1585                1590                1595                1600

Lys Val Pro Gln Leu Lys Val Ala Glu Ser Ala Gln Ser Pro Ala Ala
                1605                1610                1615

Ala His Thr Thr Asp Thr Ala Gly Tyr Asn Ala Met Glu Glu Ser Val
            1620                1625                1630

Ser Arg Glu Lys Pro Glu Leu Thr Ala Ser Thr Glu Arg Val Asn Lys
        1635                1640                1645

Arg Met Ser Met Val Val Ser Gly Leu Thr Pro Glu Glu Phe Met Leu
    1650                1655                1660
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Val Tyr Lys Phe Ala Arg Lys His His Ile Thr Leu Thr Asn Leu Ile
1665 1670 1675 1680

Thr Gln Gln Thr Thr His Val Val Met Lys Thr Asp Ala Glu Phe Val
1685 1690 1695

Cys Glu Arg Thr Leu Lys Tyr Phe Leu Gly Ile Ala Gly Gly Lys Trp
1700 1705 1710

Val Val Ser Tyr Phe Trp Val Thr Gln Ser Ile Lys Glu Arg Lys Met
1715 1720 1725

Leu Asn Glu His Asp Phe Gln Val Arg Gly Asp Val Val Asn Gly Arg
1730 1735 1740

Asn His Gln Gly Pro Lys Arg Ala Arg Glu Ser Gln Asp Arg Lys Ile
1745 1750 1755 1760

Phe Arg Gly Leu Glu Ile Cys Cys Tyr Gly Pro Phe Thr Asn Met Pro
1765 1770 1775

Thr Asp Gln Leu Glu Trp Met Val Gln Leu Cys Gly Ala Ser Val Val
1780 1785 1790

Lys Gln Leu Ser Ser Phe Thr Leu Gly Thr Gly Val His Pro Ile Val
1795 1800 1805

Val Val Gln Pro Asp Ala Trp Thr Glu Asp Asn Gly Phe His Ala Ile
1810 1815 1820

Gly Gln Met Cys Glu Ala Pro Val Val Thr Arg Gln Trp Val Leu Asp
1825 1830 1835 1840

Ser Val Ala Leu Tyr Gln Cys Gln Glu Leu Asp Thr Tyr Leu Ile Pro
1845 1850 1855

Gln Ile Pro His Ser His Tyr
1860

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(v i i) IMMEDIATE SOURCE:
(B) CLONE: s754 A

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CTAGCCTGGG CAACAAACGA 20

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(v i i) IMMEDIATE SOURCE:

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(B) CLONE: s754 B

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:4:

GCAGGAAGCA GGAATGGAAC 20

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(v i i) IMMEDIATE SOURCE:
(B) CLONE: s975 A

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:5:

TAGGAGATGG ATTATTGGTG 20

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(v i i) IMMEDIATE SOURCE:
(B) CLONE: s975 B

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:6:

AGGCAACTTT GCAATGAGTG 20

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(v i i) IMMEDIATE SOURCE:
(B) CLONE: tdj1474 A

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CAGAGTGAGA CCTTGTCTCA AA 22

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs

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(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(v i i) IMMEDIATE SOURCE:
(B) CLONE: tdj1474 B

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:8:

TTCTGCAAAC ACCTTAAACT CAG 23

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(v i i) IMMEDIATE SOURCE:
(B) CLONE: tdj1239 A

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:9:

AACCTGGAAG GCAGAGGTTG 20

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(v i i) IMMEDIATE SOURCE:
(B) CLONE: tdj1239 B

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:10:

TCTGTACCTG CTAAGCAGTG G 21

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: cDNA

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

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        ( i x ) FEATURE:
                ( A ) NAME/KEY: CDS
                ( B ) LOCATION: 2..111

        ( x i ) SEQUENCE DESCRIPTION: SEQ ID NO:11:

G GKC TTA CTC TGT TGT CCC AGC TGG AGT ACA GWG TGC GAT CAT GAG            46
  Xaa Leu Leu Cys Cys Pro Ser Trp Ser Thr Xaa Cys Asp His Gln
  1865                1870                1875

GCT TAC TGT TGC TTG ACT CCT AGG CTC AAG CGA TCC TAT CAC CTC AGT          94
Ala Tyr Cys Cys Leu Thr Pro Arg Leu Lys Arg Ser Tyr His Leu Ser
1880                1885                1890                1895

CTC CAA GTA GCT GGA  CT                                                 111
Leu Gln Val Ala Gly
                1900


( 2 ) INFORMATION FOR SEQ ID NO:12:

        ( i ) SEQUENCE CHARACTERISTICS:
                ( A ) LENGTH: 36 amino acids
                ( B ) TYPE: amino acid
                ( D ) TOPOLOGY: linear

        ( i i ) MOLECULE TYPE: protein

        ( x i ) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Xaa Leu Leu Cys Cys Pro Ser Trp Ser Thr Xaa Cys Asp His Gln Ala
  1               5                   10                  15

Tyr Cys Cys Leu Thr Pro Arg Leu Lys Arg Ser Tyr His Leu Ser Leu
            20                  25                  30

Gln Val Ala Gly
        35


( 2 ) INFORMATION FOR SEQ ID NO:13:

        ( i ) SEQUENCE CHARACTERISTICS:
                ( A ) LENGTH: 1534 base pairs
                ( B ) TYPE: nucleic acid
                ( C ) STRANDEDNESS: double
                ( D ) TOPOLOGY: linear

        ( i i ) MOLECULE TYPE: DNA (genomic)

      ( i i i ) HYPOTHETICAL: NO

        ( i v ) ANTI-SENSE: NO

        ( v i ) ORIGINAL SOURCE:
                ( A ) ORGANISM: Homo sapiens

        ( x i ) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GAGGCTAGAG GGCAGGCACT TTATGGCAAA CTCAGGTAGA ATTCTTCCTC TTCCGTCTCT          60

TTCCTTTTAC GTCATCGGGG AGACTGGGTG GCAATCGCAG CCCGAGAGAC GCATGGCTCT         120

TTCTGCCCTC CATCCTCTGA TGTACCTTGA TTTCGTATTC TGAGAGGCTG CTGCTTAGCG         180

GTAGCCCCTT GGTTTCCGTG GCAACGGAAA AGCGCGGGAA TTACAGATAA ATTAAAACTG         240

CGACTGCGCG GCGTGAGCTC GCTGAGACTT CCTGGACCCC GCACCAGGCT GTGGGGTTTC         300

TCAGATAACT GGGCCCCTGC GCTCAGGAGG CCTTCACCCT CTGCTCTGGG TAAAGGTAGT         360

AGAGTCCCGG GAAAGGGACA GGGGGCCCAA GTGATGCTCT GGGGTACTGG CGTGGGAGAG         420

TGGATTTCCG AAGCTGACAG ATGGGTATTC TTTGACGGGG GGTAGGGGCG GAACCTGAGA         480

GGCGTAAGGC GTTTGTAACC CTGGGGAGGG GGGCAGTTTG TAGGTCGCGA GGGAAGCGCT         540

GAGGATCAGG AAGGGGGCAC TGAGTGTCCG TGGGGGAATC CTCGTGATAG GAACTGGAAT         600
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ATGCCTTGAG GGGGACACTA TGTCTTTAAA AACGTCGGCT GGTCATGAGG TCAGGAGTTC 6[illegible]

CAGACCAGCC TGACCAACGT GGTGAAACTC CGTCTCTACT AAAAATACNA AAATTAGCCG 720

GGCGTGGTGC CGCTCCAGCT ACTCAGGAGG CTGAGGCAGG AGAATCGCTA GAACCCGGGA 780

GGCGGAGGTT GCAGTGAGCC GAGATCGCGC CATTGCACTC CAGCCTGGGC GACAGAGCGA 840

GACTGTCTCA AAACAAAACA AAACAAAACA AAACAAAAAA CACCGGCTGG TATGTATGAG 900

AGGATGGGAC CTTGTGGAAG AAGAGGTGCC AGGAATATGT CTGGGAAGGG GAGGAGACAG 960

GATTTTGTGG GAGGGAGAAC TTAAGAACTG GATCCATTTG CGCCATTGAG AAAGCGCAAG 1020

AGGGAAGTAG AGGAGCGTCA GTAGTAACAG ATGCTGCCGG CAGGGATGTG CTTGAGGAGG 1080

ATCCAGAGAT GAGAGCAGGT CACTGGGAAA GGTTAGGGGC GGGGAGGCCT TGATTGGTGT 1140

TGGTTTGGTC GTTGTTGATT TTGGTTTTAT GCAAGAAAAA GAAAACAACC AGAAACATTG 1200

GAGAAAGCTA AGGCTACCAC CACCTACCCG GTCAGTCACT CCTCTGTAGC TTTCTCTTTC 1260

TTGGAGAAAG GAAAAGACCC AAGGGGTTGG CAGCGATATG TGAAAAAATT CAGAATTTAT 1320

GTTGTCTAAT TACAAAAAGC AACTTCTAGA ATCTTTAAAA ATAAAGGACG TTGTCATTAG 1380

TTCTTCTGGT TTGTATTATT CTAAAACCTT CCAAATCTTC AAATTTACTT TATTTTAAAA 1440

TGATAAAATG AAGTTGTCAT TTTATAAACC TTTTAAAAAG ATATATATAT ATGTTTTTCT 1500

AATGTGTTAA AGTTCATTGG AACAGAAAGA AATG 1534

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1934 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:14:

GAGGCTAGAG GGCAGGCACT TTATGGCAAA CTCAGGTAGA ATTCTTCCTC TTCCGTCTCT 60

TTCCTTTTAC GTCATCGGGG AGACTGGGTG GCAATCGCAG CCCGAGAGAC GCATGGCTCT 120

TTCTGCCCTC CATCCTCTGA TGTACCTTGA TTTCGTATTC TGAGAGGCTG CTGCTTAGCG 180

GTAGCCCCTT GGTTTCCGTG GCAACGGAAA AGCGCGGGAA TTACAGATAA ATTAAAACTG 240

CGACTGCGCG GCGTGAGCTC GCTGAGACTT CCTGGACCCC GCACCAGGCT GTGGGGTTTC 300

TCAGATAACT GGGCCCCTGC GCTCAGGAGG CCTTCACCCT CTGCTCTGGG TAAAGGTAGT 360

AGAGTCCCGG GAAAGGGACA GGGGGCCCAA GTGATGCTCT GGGGTACTGG CGTGGGAGAG 420

TGGATTTCCG AAGCTGACAG ATGGGTATTC TTTGACGGGG GGTAGGGGCG GAACCTGAGA 480

GGCGTAAGGC GTTGTGAACC CTGGGGAGGG GGGCAGTTTG TAGGTCGCGA GGGAAGCGCT 540

GAGGATCAGG AAGGGGGCAC TGAGTGTCCG TGGGGGAATC CTCGTGATAG GAACTGGAAT 600

ATGCCTTGAG GGGGACACTA TGTCTTTAAA AACGTCGGCT GGTCATGAGG TCAGGAGTTC 660

CAGACCAGCC TGACCAACGT GGTGAAACTC CGTCTCTACT AAAAATACNA AAATTAGCCG 720

GGCGTGGTGC CGCTCCAGCT ACTCAGGAGG CTGAGGCAGG AGAATCGCTA GAACCCGGGA 780

GGCGGAGGTT GCAGTGAGCC GAGATCGCGC CATTGCACTC CAGCCTGGGC GACAGAGCGA 840

-continued

GACTGTCTCA AAACAAAACA AAACAAAACA AAACAAAAAA CACCGGCTGG TATGTATGAG 900

AGGATGGGAC CTTGTGGAAG AAGAGGTGCC AGGAATATGT CTGGGAAGGG GAGGAGACAG 960

GATTTTGTGG GAGGGAGAAC TTAAGAACTG GATCCATTTG CGCCATTGAG AAAGCGCAAG 1020

AGGGAAGTAG AGGAGCGTCA GTAGTAACAG ATGCTGCCGG CAGGGATGTG CTTGAGGAGG 1080

ATCCAGAGAT GAGAGCAGGT CACTGGGAAA GGTTAGGGGC GGGGAGGCCT TGATTGGTGT 1140

TGGTTTGGTC GTTGTTGATT TTGGTTTTAT GCAAGAAAAA GAAAACAACC AGAAACATTG 1200

GAGAAAGCTA AGGCTACCAC CACCTACCCG GTCAGTCACT CCTCTGTAGC TTTCTCTTTC 1260

TTGGAGAAAG GAAAAGACCC AAGGGGTTGG CAGCGATATG TGAAAAAATT CAGAATTTAT 1320

GTTGTCTAAT TACAAAAAGC AACTTCTAGA ATCTTTAAAA ATAAAGGACG TTGTCATTAG 1380

TTCTTCTGGT TTGTATTATT CTAAAACCTT CCAAATCTTC AAATTTACTT TATTTTAAAA 1440

TGATAAAATG AAGTTGTCAT TTTATAAACC TTTTAAAAAG ATATATATAT ATGTTTTTCT 1500

AATGTGTTAA AGTTCATTGG AACAGAAAGA AATGGATTTA TCTGCTCTTC GCGTTGAAGA 1560

AGTACAAAAT GTCATTAATG CTATGCAGAA AATCTTAGAG TGTCCCATCT GGTAAGTCAG 1620

CACAAGAGTG TATTAATTTG GGATTCCTAT GATTATCTCC TATGCAAATG AACAGAATTG 1680

ACCTTACATA CTAGGGAAGA AAAGACATGT CTAGTAAGAT TAGGCTATTG TAATTGCTGA 1740

TTTTCTTAAC TGAAGAACTT TAAAAATATA GAAAATGATT CCTTGTTCTC CATCCACTCT 1800

GCCTCTCCCA CTCCTCTCCT TTTCAACACA ATCCTGTGGT CCGGGAAAGA CAGGGCTCTG 1860

TCTTGATTGG TTCTGCACTG GGCAGGATCT GTTAGATACT GCATTTGCTT TCTCCAGCTC 1920

TAAA 1924

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 631 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:15:

AAATGCTGAT GATAGTATAG AGTATTGAAG GGATCAATAT AATTCTGTTT TGATATCTGA 60

AAGCTCACTG AAGGTAAGGA TCGTATTCTC TGCTGTATTC TCAGTTCCTG ACACAGCAGA 120

CATTTAATAA ATATTGAACG AACTTGAGGC CTTATGTTGA CTCAGTCATA ACAGCTCAAA 180

GTTGAACTTA TTCACTAAGA ATAGCTTTAT TTTTAAATAA ATTATTGAGC CTCATTTATT 240

TTCTTTTTCT CCCCCCCCTA CCCTGCTAGT CTGGAGTTGA TCAAGGAACC TGTCTCCACA 300

AAGTGTGACC ACATATTTTG CAAGTAAGTT TGAATGTGTT ATGTGGCTCC ATTATTAGCT 360

TTTGTTTTTG TCCTTCATAA CCCAGGAAAC ACCTAACTTT ATAGAAGCTT TACTTTCTTC 420

AATTAAGTGA GAACGAAAAT CCAACTCCAT TTCATTCTTT CTCAGAGAGT ATATAGTTAT 480

CAAAAGTTGG TTGTAATCAT AGTTCCTGGT AAAGTTTTGA CATATATTAT CTTTTTTTTT 540

TTTTGAGACA AGTCTCGCTC TGTCGCCCAG GCTGGAGTGC AGTGGCATGA GGCTTGCTCA 600

CTGCACCTCC GCCCCCGAGT TCAGCGACTC T 631

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(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 481 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
TGAGATCTAG ACCACATGGT CAAAGAGATA GAATGTGAGC AATAAATGAA CCTTAAATTT    60
TTCAACAGCT ACTTTTTTTT TTTTTTTTTG AGACAGGGKC TTACTCTGTT GTCCCAGCTG   120
GAGTACAGWG TGCGATCATG AGGCTTACTG TTGCTTGACT CCTAGGCTCA AGCGATCCTA   180
TCACCTCAGT CTCCAAGTAG CTGGACTGTA AGTGCACACC ACCATATCCA GCTAAATTTT   240
GTGTTTTCTG TAGAGACGGG GTTTCGCCAT GTTTCCCAGG CTGGTCTTGA ACTTTGGGCT   300
TAACCCGTCT GCCCACCTAG GCATCCCAAA GTGCTAGGAT TACAGGTGTG AGTCATCATG   360
CCTGGCCAGT ATTTTAGTTA GCTCTGTCTT TTCAAGTCAT ATACAAGTTC ATTTTCTTTT   420
AAGTTTAGTT AACAACCTTA TATCATGTAT TCTTTTCTAG CATAAAGAAA GATTCGAGGC   480
C                                                                   481
```

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 522 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
TGTGATCATA ACAGTAAGCC ATATGCATGT AAGTTCAGTT TTCATAGATC ATTGCTTATG    60
TAGTTTAGGT TTTTGCTTAT GCAGCATCCA AAAACAATTA GGAAACTATT GCTTGTAATT   120
CACCTGCCAT TACTTTTTAA ATGGCTCTTA AGGGCAGTTG TGAGATTATC TTTTCATGGC   180
TATTTGCCTT TTGAGTATTC TTTCTACAAA AGGAAGTAAA TTAAATTGTT CTTTCTTTCT   240
TTATAATTTA TAGATTTTGC ATGCTGAAAC TTCTCAACCA GAAGAAAGGG CCTTCACAGT   300
GTCCTTTATG TAAGAATGAT ATAACCAAAA GGTATATAAT TTGGTAATGA TGCTAGGTTG   360
GAAGCAACCA CAGTAGGAAA AAGTAGAAAT TATTTAATAA CATAGCGTTC CTATAAAACC   420
ATTCATCAGA AAAATTTATA AAAGAGTTTT TAGCACACAG TAAATTATTT CCAAAGTTAT   480
TTTCCTGAAA GTTTTATGGG CATCTGCCTT ATACAGGTAT TG                      522
```

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

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(A) LENGTH: 465 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:18:

GGTAGGCTTA AATGAATGAC AAAAAGTTAC TAAATCACTG CCATCACACG GTTTATACAG 60

ATGTCAATGA TGTATTGATT ATAGAGGTTT TCTACTGTTG CTGCATCTTA TTTTTATTTG 120

TTTACATGTC TTTTCTTATT TTAGTGTCCT TAAAAGGTTG ATAATCACTT GCTGAGTGTG 180

TTTCTCAAAC AATTTAATTT CAGGAGCCTA CAAGAAAGTA CGAGATTTAG TCAACTTGTT 240

GAAGAGCTAT TGAAAATCAT TTGTGCTTTT CAGCTTGACA CAGGTTTGGA GTGTAAGTGT 300

TGAATATCCC AAGAATGACA CTCAAGTGCT GTCCATGAAA ACTCAGGAAG TTTGCACAAT 360

TACTTTCTAT GACGTGGTGA TAAGACCTTT TAGTCTAGGT TAATTTTAGT TCTGTATCTG 420

TAATCTATTT TAAAAAATTA CTCCCACTGG TCTCACACCT TATTT 465

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:19:

AAAAAATCAC AGGTAACCTT AATGCATTGT CTTAACACAA CAAAGAGCAT ACATAGGGTT 60

TCTCTTGGTT TCTTTGATTA TAATTCATAC ATTTTTCTCT AACTGCAAAC ATAATGTTTT 120

CCCTTGTATT TTACAGATGC AAACAGCTAT AATTTTGCAA AAAAGGAAAA TAACTCTCCT 180

GAACATCTAA AAGATGAAGT TTCTATCATC CAAAGTATGG GCTACAGAAA CCGTGCCAAA 240

AGACTTCTAC AGAGTGAACC CGAAAATCCT TCCTTGGTAA AACCATTTGT TTTCTTCTTC 300

TTCTTCTTCT TCTTTTCTTT TTTTTTTCTT TTTTTTTTTG AGATGGAGTC TTGCTCTGTG 360

GCCCAGGCTA GAAGCAGTCC TCCTGCCTTA GCCNCCTTAG TAGCTGGGAT TACAGGCACG 420

CGCACCATGC CAGGCTAATT TTTGTATTTT TAGTAGAGAC GGGGTTTCAT CATGTTGGCC 480

AGGCTGGTCT CGAACTCCTA ACCTCAGGTG ATC 513

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6769 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

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(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:20:

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ATGATGGAGA TCTTAAAAAG TAATCATTCT GGGGCTGGGC GTAGTAGCTT GCACCTGTAA    60
TCCCAGCACT TCGGGAGGCT GAGGCAGGCA GATAATTTGA GGTCAGGAGT TTGAGACCAG   120
CCTGGCCAAC ATGGTGAAAC CCATCTCTAC TAAAAATACA AAAATTAGCT GGGTGTGGTG   180
GCACGTACCT GTAATCCCAG CTACTCGGGA GGCGGAGGCA CAAGAATTGC TTGAACCTAG   240
GACGCGGAGG TTGCAGCGAG CCAAGATCGC GCCACTGCAC TCCAGCCTGG GCCGTAGAGT   300
GAGACTCTGT CTCAAAAAAG AAAAAAAAGT AATTGTTCTA GCTGGGCGCA GTGGCTCTTG   360
CCTGTAATCC CAGCACTTTG GGAGGCCAAG GCGGGTGGAT CTCGAGTCCT AGAGTTCAAG   420
ACCAGCCTAG GCAATGTGGT GAAACCCCAT CGCTACAAAA AATACAAAAA TTAGCCAGGC   480
ATGGTGGCGT GCGCATGTAG TCCCAGCTCC TTGGGAGGCT GAGGTGGGAG GATCACTTGA   540
ACCCAGGAGA CAGAGGTTGC AGTGAACCGA GATCACGCCA CCACGCTCCA GCCTGGGCAA   600
CAGAACAAGA CTCTGTCTAA AAAAATACAA ATAAAATAAA AGTAGTTCTC ACAGTACCAG   660
CATTCATTTT TCAAAAGATA TAGAGCTAAA AAGGAAGGAA AAAAAAAGTA ATGTTGGGCT   720
TTTAAATACT CGTTCCTATA CTAAATGTTC TTAGGAGTGC TGGGGTTTTA TTGTCATCAT   780
TTATCCTTTT TAAAAATGTT ATTGGCCAGG CACGGTGGCT CATGGCTGTA ATCCCAGCAC   840
TTTGGGAGGC CGAGGCAGGC AGATCACCTG AGGTCAGGAG TGTGAGACCA GCCTGGCCAA   900
CATGGCGAAA CCTGTCTCTA CTAAAAATAC AAAAATTAAC TAGGCGTGGT GGTGTACGCC   960
TGTAGTCCCA GCTACTCGGG AGGCTGAGGC AGGAGAATCA ACTGAACCAG GGAGGTGGAG  1020
GTTGCAGTGT GCCGAGATCA CGCCACTGCA CTCTAGCCTG GCAACAGAGC AAGATTCTGT  1080
CTCAAAAAAA AAAAACATAT ATACACATAT ATCCCAAAGT GCTGGGATTA CATATATATA  1140
TATATATATA TATTATATAT ATATATATAT ATATATGTGA TATATATGTG ATATATATAT  1200
AACATATATA TATGTAATAT ATATGTGATA TATATATAAT ATATATATGT AATATATATG  1260
TGATATATAT ATATACACAC ACACACACAT ATATATGTAT GTGTGTGTAC ACACACACAC  1320
ACAAATTAGC CAGGCATAGT TGCACACGCT TGGTAGACCC AGCTACTCAG GAGGCTGAGG  1380
GAGGAGAATC TCTTGAACTT AGGAGGCGGA GGTTGCAGTG AGCTGAGATT GCGCCACTGC  1440
ACTCCAGCCT GGGTGACAGA GCAGGACTCT GTACACCCCC CAAAACAAAA AAAAAAGTTA  1500
TCAGATGTGA TTGGAATGTA TATCAAGTAT CAGCTTCAAA ATATGCTATA TTAATACTTC  1560
AAAAATTACA CAAATAATAC ATAATCAGGT TTGAAAAATT TAAGACAACM RAARAAAAAA  1620
WYCMAATCAC AMATATCCCA CACATTTTAT TATTMCTMCT MCWATTATTT TGWAGAGMCT  1680
GGGTCTCACY CYRTTGCTWA TGCTG
GTCTT TGAACYCCYK GCCYCAARCA RTCCTSCTCC  1740
ABCCTCCCAA RGTGCTGGGG ATWATAGGCA TGARCTAACC GCACCCAGCC CCAGACATTT  1800
TAGTGTGTAA ATTCCTGGGC ATTTTTTCAA GGCATCATAC ATGTTAGCTG ACTGATGATG  1860
GTCAATTTAT TTTGTCCATG GTGTCAAGTT TCTCTTCAGG AGGAAAAGCA CAGAACTGGC  1920
CAACAATTGC TTGACTGTTC TTTACCATAC TGTTTAGCAG GAAACCAGTC TCAGTGTCCA  1980
ACTCTCTAAC CTTGGAACTG TGAGAACTCT GAGGACAAAG CAGCGGATAC AACCTCAAAA  2040
GACGTCTGTC TACATTGAAT TGGGTAAGGG TCTCAGGTTT TTTAAGTATT TAATAATAAT  2100
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TGCTGGATTC CTTATCTTAT AGTTTTGCCA AAAATCTTGG TCATAATTTG TATTTGTGGT   2160
AGGCAGCTTT GGGAAGTGAA TTTTATGAGC CCTATGGTGA GTTATAAAAA ATGTAAAAGA   2220
CGCAGTTCCC ACCTTGAAGA ATCTTACTTT AAAAAGGGAG CAAAAGAGGC CAGGCATGGT   2280
GGCTCACACC TGTAATCCCA GCACTTTGGG AGGCCAAAGT GGGTGGATCA CCTGAGGTCG   2340
GGAGTTCGAG ACCAGCCTAG CCAACATGGA GAAACTCTGT CTGTACCAAA AAATAAAAAA   2400
TTAGCCAGGT GTGGTGGCAC ATAACTGTAA TCCCAGCTAC TCGGGAGGCT GAGGCAGGAG   2460
AATCACTTGA ACCCGGGAGG TGGAGGTTGC GGTGAACCGA GATCGCACCA TTGCACTCCA   2520
GCCTGGGCAA AAATAGCGAA ACTCCATCTA AAAAAAAAAA AGAGAGCAAA AGAAAGAMTM   2580
TCTGGTTTTA AMTMTGTGTA AATATGTTTT TGGAAAGATG GAGAGTAGCA ATAAGAAAAA   2640
ACATGATGGA TTGCTACAGT ATTTAGTTCC AAGATAAATT GTACTAGATG AGGAAGCCTT   2700
TTAAGAAGAG CTGAATTGCC AGGCGCAGTG GCTCACGCCT GTAATCCCAG CACTTTGGGA   2760
GGCCGAGGTG GGCGGATCAC CTGAGGTCGG GAGTTCAAGA CCAGCCTGAC CAACATGGAG   2820
AAACCCCATC TCTACTAAAA AAAAAAAAAA AAAAATTAGC CGGGGTGGTG GCTTATGCCT   2880
GTAATCCCAG CTACTCAGGA GGCTGAGGCA GGAGAATCGC TTGAACCCAG GAAGCAGAGG   2940
TTGCAGTGAG CCAAGATCGC ACCATTGCAC TCCAGCCTAG GCAACAAGAG TGAAACTCCA   3000
TCTCAAAAAA AAAAAAAAAG AGCTGAATCT TGGCTGGGCA GGATGGCTCG TGCCTGTAAT   3060
CCTAACGCTT TGGAAGACCG AGGCAGAAGG ATTGGTTGAG TCCACGAGTT TAAGACCAGC   3120
CTGGCCAACA TAGGGGAACC CTGTCTCTAT TTTTAAAATA ATAATACATT TTTGGCCGGT   3180
GCGGTGGCTC ATGCCTGTAA TCCCAATACT TTGGGAGGCT GAGGCAGGTA GATCACCTGA   3240
GGTCAGAGTT CGAGACCAGC CTGGATAACC TGGTGAAACC CCTCTTTACT AAAAATACAA   3300
AAAAAAAAAA AAATTAGCTG GGTGTGGTAG CACATGCTTG TAATCCCAGC TACTTGGGAG   3360
GCTGAGGCAG GAGAATCGCT TGAACCAGGG AGGCGGAGGT TACAATGAGC CAACACTACA   3420
CCACTGCACT CCAGCCTGGG CAATAGAGTG AGACTGCATC TCAAAAAAAT AATAATTTTT   3480
AAAAATAATA AATTTTTTTA AGCTTATAAA AAGAAAAGTT GAGGCCAGCA TAGTAGCTCA   3540
CATCTGTAAT CTCAGCAGTG GCAGAGGATT GCTTGAAGCC AGGAGTTTGA GACCAGCCTG   3600
GGCAACATAG CAAGACCTCA TCTCTACAAA AAAATTTCTT TTTTAAATTA GCTGGGTGTG   3660
GTGGTGTGCA TCTGTAGTCC CAGCTACTCA GGAGGCAGAG GTGAGTGGAT ACATTGAACC   3720
CAGGAGTTTG AGGCTGTAGT GAGCTATGAT CATGCCACTG CACTCCAACC TGGGTGACAG   3780
AGCAAGACCT CCAAAAAAAA AAAAAAAAGA GCTGCTGAGC TCAGAATTCA AACTGGGCTC   3840
TCAAATTGGA TTTTCTTTTA GAATATATTT ATAATTAAAA AGGATAGCCA TCTTTTGAGC   3900
TCCCAGGCAC CACCATCTAT TTATCATAAC ACTTACTGTT TTCCCCCCTT ATGATCATAA   3960
ATTCCTAGAC AACAGGCATT GTAAAAATAG TTATAGTAGT TGATATTTAG GAGCACTTAA   4020
CTATATTCCA GGCACTATTG TGCTTTTCTT GTATAACTCA TTAGATGCTT GTCAGACCTC   4080
TGAGATTGTT CCTATTATAC TTATTTTACA GATGAGAAAA TTAAGGCACA GAGAAGTTAT   4140
GAAATTTTTC CAAGGTATTA AACCTAGTAA GTGGCTGAGC CATGATTCAA ACCTAGGAAG   4200
TTAGATGTCA GAGCCTGTGC TTTTTTTTTG TTTTTGTTTT TGTTTTCAGT AGAAACGGGG   4260
GTCTCACTTT GTTGGCCAGG CTGGTCTTGA ACTCCTAACC TCAAATAATC CACCCATCTC   4320
GGCCTCCTCA AGTGCTGGGA TTACAGGTGA GAGCCACTGT GCCTGGCGAA GCCCATGCCT   4380
TTAACCACTT CTCTGTATTA CATACTAGCT TAACTAGCAT TGTACCTGCC ACAGTAGATG   4440
CTCAGTAAAT ATTTCTAGTT GAATATCTGT TTTTCAACAA GTACATTTTT TTAACCCTTT   4500
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TAATTAAGAA AACTTTTATT GATTTATTTT TTGGGGGGAA ATTTTTTAGG ATCTGATTCT    4560

TCTGAAGATA CCGTTAATAA GGCAACTTAT TGCAGGTGAG TCAAAGAGAA CCTTTGTCTA    4620

TGAAGCTGGT ATTTTCCTAT TTAGTTAATA TTAAGGATTG ATGTTTCTCT CTTTTTAAAA    4680

ATATTTTAAC TTTTATTTTA GGTTCAGGGA TGTATGTGCA GTTTGTTATA TAGGTAAACA    4740

CACGACTTGG GATTTGGTGT ATAGATTTTT TTCATCATCC GGGTACTAAG CATACCCCAC    4800

AGTTTTTTGT TTGCTTTCTT TCTGAATTTC TCCCTCTTCC CACCTTCCTC CCTCAAGTAG    4860

GCTGGTGTTT CTCCAGACTA GAATCATGGT ATTGGAAGAA ACCTTAGAGA TCATCTAGTT    4920

TAGTTCTCTC ATTTTATAGT GGAGGAAATA CCCTTTTTGT TTGTTGGATT TAGTTATTAG    4980

CACTGTCCAA AGGAATTTAG GATAACAGTA GAACTCTGCA CATGCTTGCT TCTAGCAGAT    5040

TGTTCTCTAA GTTCCTCATA TACAGTAATA TTGACACAGC AGTAATTGTG ACTGATGAAA    5100

ATGTTCAAGG ACTTCATTTT CAACTCTTTC TTTCCTCTGT TCCTTATTTC CACATATCTC    5160

TCAAGCTTTG TCTGTATGTT ATATAATAAA CTACAAGCAA CCCCAACTAT GTTACCTACC    5220

TTCCTTAGGA ATTATTGCTT GACCCAGGTT TTTTTTTTTT TTTTTTTGGA GACGGGGTCT    5280

TGCCCTGTTG CCAGGATGGA GTGTAGTGGC GCCATCTCGG CTCACTGCAA TCTCCAACTC    5340

CCTGGTTCAA GCGATTCTCC TGTCTCAATC TCACGAGTAG CTGGGACTAC AGGTATACAC    5400

CACCACGCCC GGTTAATTGA CCATTCCATT TCTTTCTTTC TCTCTTTTTT TTTTTTTTTT    5460

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CGCAACGTCT GCCTCCCAGG TTGAAGCCAT ACTCCTGCCT CAGCCTCTCT AGTAGCTGGG    5580

ACTACAGGCG CGCGCCACCA CACCCGGCTA ATTTTTGTAT TTTTAGTAGA GATGGGGTTT    5640

CACCATGTTG GCCAGGCTGG TCTTGAACTC ATGACCTCAA GTGGTCCACC CGCCTCAGCC    5700

TCCCAAAGTG CTGGAATTAC AGGCTTGAGC CACCGTGCCC AGCAACCATT TCATTTCAAC    5760

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TAATCGAAAG AGCTAAAATG TTTGATCTTG GTCATTTGAC AGTTCTGCAT ACATGTAACT    5880

AGTGTTTCTT ATTAGGACTC TGTCTTTTCC CTATAGTGTG GGAGATCAAG AATTGTTACA    5940

AATCACCCCT CAAGGAACCA GGGATGAAAT CAGTTTGGAT TCTGCAAAAA AGGGTAATGG    6000

CAAAGTTTGC CAACTTAACA GGCACTGAAA AGAGAGTGGG TAGATACAGT ACTGTAATTA    6060

GATTATTCTG AAGACCATTT GGGACCTTTA CAACCCACAA AATCTCTTGG CAGAGTTAGA    6120

GTATCATTCT CTGTCAAATG TCGTGGTATG GTCTGATAGA TTTAAATGGT ACTAGACTAA    6180

TGTACCTATA ATAAGACCTT CTTGTAACTG ATTGTTGCCC TTTCGCTTTT TTTTTTGTTT    6240

GTTTGTTTGT TTTTTTTTGA GATGGGGTCT CACTCTGTTG CCCAGGCTGG AGTGCAGTGA    6300

TGCAATCTTG GCTCACTGCA ACCTCCACCT CCAAAGGCTC AAGCTATCCT CCCACTTCAG    6360

CCTCCTGAGT AGCTGGGACT ACAGGCGCAT GCCACCACAC CCGGTTAATT TTTTGTGGTT    6420

TTATAGAGAT GGGGTTTCAC CATGTTACCG AGGCTGGTCT CAAACTCCTG GACTCAAGCA    6480

GTCTGCCCAC TTCAGCCTCC CAAAGTGCTG CAGTTACAGG CTTGAGCCAC TGTGCCTGGC    6540

CTGCCCTTTA CTTTTAATTG GTGTATTTGT GTTTCATCTT TTACCTACTG GTTTTTAAAT    6600

ATAGGGAGTG GTAAGTCTGT AGATAGAACA GAGTATTAAG TAGACTTAAT GGCCAGTAAT    6660

CTTTAGAGTA CATCAGAACC AGTTTTCTGA TGGCCAATCT GCTTTTAATT CACTCTTAGA    6720

CGTTAGACAA ATAGGTGTGG TTTCTGCATA GGGAAAATTC TGAAATTAA                6769
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(2) INFORMATION FOR SEQ ID NO:21:

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(i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 4240 base pairs
  (B) TYPE: nucleic acid
  (C) STRANDEDNESS: double
  (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
  (A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:21:

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GATCCTAAGT GGAAATAATC TAGGTAAATA GGAATTAAAT GAAAGAGTAT GAGCTACATC      60

TTCAGTATAC TTGGTAGTTT ATGAGGTTAG TTTCTCTAAT ATAGCCAGTT GGTTGATTTC     120

CACCTCCAAG GTGTATGAAG TATGTATTTT TTTAATGACA ATTCAGTTTT TGAGTACCTT     180

GTTATTTTTG TATATTTTCA GCTGCTTGTG AATTTTCTGA GACGGATGTA ACAAATACTG     240

AACATCATCA ACCCAGTAAT AATGATTTGA ACACCACTGA GAAGCGTGCA GCTGAGAGGC     300

ATCCAGAAAA GTATCAGGGT AGTTCTGTTT CAAACTTGCA TGTGGAGCCA TGTGGCACAA     360

ATACTCATGC CAGCTCATTA CAGCATGAGA ACAGCAGTTT ATTACTCACT AAAGACAGAA     420

TGAATGTAGA AAAGGCTGAA TTCTGTAATA AAAGCAAACA GCCTGGCTTA GCAAGGAGCC     480

AACATAACAG ATGGGCTGGA AGTAAGGAAA CATGTAATGA TAGGCGGACT CCCAGCACAG     540

AAAAAAAGGT AGATCTGAAT GCTGATCCCC TGTGTGAGAG AAAAGAATGG AATAAGCAGA     600

AACTGCCATG CTCAGAGAAT CCTAGAGATA CTGAAGATGT TCCTTGGATA ACACTAAATA     660

GCAGCATTCA GAAAGTTAAT GAGTGGTTTT CCAGAAGTGA TGAACTGTTA GGTTCTGATG     720

ACTCACATGA TGGGGAGTCT GAATCAAATG CCAAAGTAGC TGATGTATTG GACGTTCTAA     780

ATGAGGTAGA TGAATATTCT GGTTCTTCAG AGAAAATAGA CTTACTGGCC AGTGATCCTC     840

ATGAGGCTTT AATATGTAAA AGTGAAAGAG TTCACTCCAA ATCAGTAGAG AGTAATATTG     900

AAGGCCAAAT ATTTGGGAAA ACCTATCGGA AGAAGGCAAG CCTCCCCAAC TTAAGCCATG     960

TAACTGAAAA TCTAATTATA GGAGCATTTG TTACTGAGCC ACAGATAATA CAAGAGCGTC    1020

CCCTCACAAA TAAATTAAAG CGTAAAAGGA GACCTACATC AGGCCTTCAT CCTGAGGATT    1080

TTATCAAGAA AGCAGATTTG GCAGTTCAAA AGACTCCTGA AATGATAAAT CAGGGAACTA    1140

ACCAAACGGA GCAGAATGGT CAAGTGATGA ATATTACTAA TAGTGGTCAT GAGAATAAAA    1200

CAAAAGGTGA TTCTATTCAG AATGAGAAAA ATCCTAACCC AATAGAATCA CTCGAAAAAG    1260

AATCTGCTTT CAAAACGAAA GCTGAACCTA TAAGCAGCAG TATAAGCAAT ATGGAACTCG    1320

AATTAAATAT CCACAATTCA AAAGCACCTA AAAAGAATAG GCTGAGGAGG AAGTCTTCTA    1380

CCAGGCATAT TCATGCGCTT GAACTAGTAG TCAGTAGAAA TCTAAGCCCA CCTAATTGTA    1440

CTGAATTGCA AATTGATAGT TGTTCTAGCA GTGAAGAGAT AAAGAAAAAA AAGTACAACC    1500

AAATGCCAGT CAGGCACAGC AGAAACCTAC AACTCATGGA AGGTAAAGAA CCTGCAACTG    1560

GAGCCAAGAA GAGTAACAAG CCAAATGAAC AGACAAGTAA AAGACATGAC AGCGATACTT    1620

TCCCAGAGCT GAAGTTAACA AATGCACCTG GTTCTTTTAC TAAGTGTTCA AATACCAGTG    1680

AACTTAAAGA ATTTGTCAAT CCTAGCCTTC CAAGAGAAGA AAAAGAAGAG AACTAGAAAC    1740

AGTTAAAGTG TCTAATAATG CTGAAGACCC CAAAGATCTC ATGTTAAGTG GAGAAAGGGT    1800

TTTGCAAACT GAAAGATCTG TAGAGAGTAG CAGTATTTCA TTGGTACCTG GTACTGATTA    1860

TGGCACTCAG GAAAGTATCT CGTTACTGGA AGTTAGCACT CTAGGGAAGG CAAAAACAGA    1920
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ACCAAATAAA TGTGTGAGTC AGTGTGCAGC ATTTGAAAAC CCCAAGGGAC TAATTCATGG 1980

TTGTTCCAAA GATAATAGAA ATGACACAGA AGGCTTTAAG TATCCATTGG GACATGAAGT 2040

TAACCACAGT CGGGAAACAA GCATAGAAAT GGAAGAAAGT GAACTTGATG CTCAGTATTT 2100

GCAGAATACA TTCAAGGTTT CAAAGCGCCA GTCATTTGCT CCGTTTTCAA ATCCAGGAAA 2160

TGCAGAAGAG GAATGTGCAA CATTCTCTGC CCACTCTGGG TCCTTAAAGA AACAAAGTCC 2220

AAAAGTCACT TTTGAATGTG AACAAAAGGA AGAAAATCAA GGAAAGAATG AGTCTAATAT 2280

CAAGCCTGTA CAGACAGTTA ATATCACTGC AGGCTTTCCT GTGGTTGGTC AGAAAGATAA 2340

GCCAGTTGAT AATGCCAAAT GTAGTATCAA AGGAGGCTCT AGGTTTTGTC TATCATCTCA 2400

GTTCAGAGGC AACGAAACTG GACTCATTAC TCCAAATAAA CATGGACTTT TACAAAACCC 2460

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TCTGCTAGAG GAAAACTTTG AGGAACATTC AATGTCACCT GAAAGAGAAA TGGGAAATGA 2580

GAACATTCCA AGTACAGTGA GCACAATTAG CCGTAATAAC ATTAGAGAAA ATGTTTTTAA 2640

AGAAGCCAGC TCAAGCAATA TTAATGAAGT AGGTTCCAGT ACTAATGAAG TGGGCTCCAG 2700

TATTAATGAA ATAGGTTCCA GTGATGAAAA CATTCAAGCA GAACTAGGTA GAAACAGAGG 2760

GCCAAAATTG AATGCTATGC TTAGATTAGG GGTTTTGCAA CCTGAGGTCT ATAAACAAAG 2820

TCTTCCTGGA AGTAATTGTA AGCATCCTGA AATAAAAAAG CAAGAATATG AAGAAGTAGT 2880

TCAGACTGTT AATACAGATT TCTCTCCATA TCTGATTTCA GATAACTTAG AACAGCCTAT 2940

GGGAAGTAGT CATGCATCTC AGGTTTGTTC TGAGACACCT GATGACCTGT TAGATGATGG 3000

TGAAATAAAG GAAGATACTA GTTTTGCTGA AAAAGACATT AAGGAAAGTT CTGCTGTTTT 3060

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TAGTGAGGAT GAAGAGCTTC CCTGCTTCCA ACACTTGTTA TTTGGTAAAG TAAACAATAT 3240

ACCTTCTCAG TCTACTAGGC ATAGCACCGT TGCTACCGAG TGTCTGTCTA AGAACACAGA 3300

GGAGAATTTA TTATCATTGA AGAATAGCTT AAATGACTGC AGTAACCAGG TAATATTGGC 3360

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GATTGGTTCT TCCAAACAAA TGAGGCATCA GTCTGAAAGC CAGGGAGTTG GTCTGAGTGA 3540

CAAGGAATTG GTTTCAGATG ATGAAGAAAG AGGAACGGGC TTGGAAGAAA ATAATCAAGA 3600

AGAGCAAAGC ATGGATTCAA ACTTAGGTAT TGGAACCAGG TTTTTGTGTT TGCCCCAGTC 3660

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GTATAGTTAA AGGAACTGCT TCTTAAACTT GAAACATGTT CCTCCTAAGG TGCTTTTCAT 3780

AGAAAAAAGT CCTTCACACA GCTAGGACGT CATCTTTGAC TGAATGAGCT TTAACATCCT 3840

AATTACTGGT GGACTTACTT CTGGTTTCAT TTTATAAAGC AAATCCCGGT GTCCCAAAGC 3900

AAGGAATTTA ATCATTTTGT GTGACATGAA AGTAAATCCA GTCCTGCCAA TGAGAAGAAA 3960

AAGACACAGC AAGTTGCAGC GTTTATAGTC TGCTTTTACA TCTGAACCTC TGTTTTTGTT 4020

ATTTAAGGTG AAGCAGCATC TGGGTGTGAG AGTGAAACAA GCGTCTCTGA AGACTGCTCA 4080

GGGCTATCCT CTCAGAGTGA CATTTTAACC ACTCAGGTAA AAAGCGTGTG TGTGTGTGCA 4140

CATGCGTGTG TGTGGTGTCC TTTGCATTCA GTAGTATGTA TCCCACATTC TTAGGTTTGC 4200

TGACATCATC TCTTTGAATT AATGGCACAA TTGTTTGTGG TTCATTGTC 4249

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(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 710 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:22:

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NGNGAATGTA ATCCTAATAT TTCNCNCCNA CTTAAAAGAA TACCACTCCA ANGGCATCNC      60
AATACATCAA TCAATTGGGG AATTGGGATT TTCCCTCNCT AACATCANTG GAATAATTTC     120
ATGGCATTAA TTGCATGAAT GTGGTTAGAT TAAAAGGTGT TCATGCTAGA ACTTGTAGTT     180
CCATACTAGG TGATTTCAAT TCCTGTGCTA AAATTAATTT GTATGATATA TTNTCATTTA     240
ATGGAAAGCT TCTCAAAGTA TTTCATTTTC TTGGTACCAT TTATCGTTTT TGAAGCAGAG     300
GGATACCATG CAACATAACC TGATAAAGCT CCAGCAGGAA ATGGCTGAAC TAGAAGCTGT     360
GTTAGAACAG CATGGGAGCC AGCCTTCTAA CAGCTACCCT TCCATCATAA GTGACTCTTC     420
TGCCCTTGAG GACCTGCGAA ATCCAGAACA AAGCACATCA GAAAAAGGTG TGTATTGTTG     480
GCCAAACACT GATATCTTAA GCAAAATTCT TTCCTTCCCC TTTATCTCCT TCTGAAGAGT     540
AAGGACCTAG CTCCAACATT TTATGATCCT TGCTCAGCAC ATGGGTAATT ATGGAGCCTT     600
GGTTCTTGTC CCTGCTCACA ACTAATATAC CAGTCAGAGG GACCCAAGGC AGTCATTCAT     660
GTTGTCATCT GAGATACCTA CAACAAGTAG ATGCTATGGG GAGCCCATGG                710
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(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 473 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:23:

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CCATTGGTGC TAGCATCTGT CTGTTGCATT GCTTGTGTTT ATAAAATTCT GCCTGATATA      60
CTTGTTAAAA ACCAATTTGT GTATCATAGA TTGATGCTTT TGAAAAAAAT CAGTATTCTA     120
ACCTGAATTA TCACTATCAG AACAAAGCAG TAAAGTAGAT TTGTTTTCTC ATTCCATTTA     180
AAGCAGTATT AACTTCACAG AAAAGTAGTG AATACCCTAT AAGCCAGAAT CCAGAAGGCC     240
TTTCTGCTGA CAAGTTTGAG GTGTCTGCAG ATAGTTCTAC CAGTAAAAAT AAAGAACCAG     300
GAGTGGAAAG GTAAGAAACA TCAATGTAAA GATGCTGTGG TATCTGACAT CTTTATTTAT     360
ATTGAACTCT GATTGTTAAT TTTTTTCACC ATACTTTCTC CAGTTTTTTT GCATACAGGC     420
ATTTATACAC TTTTATTGCT CTAGGATACT TCTTTTGTTT AATCCTATAT AGG            473
```

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 421 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GGATAAGNTC AAGAGATATT TTGATAGGTG ATGCAGTGAT NAATTGNGAA AATTTNC[illegible]C 60

CTGCTTTTAA TCTTCCCCCG TTCTTTCTTC CTNCCTCCCT CCCTTCCTNC CTCCCGTCCT 120

TNCCTTTCCT TTCCCTCCCT TCCNCCTTCT TTCCNTCTNT CTTTCCTTTC TTTCCTGTCT 180

ACCTTTCTTT CCTTCCTCCC [illegible]CCTTTTCT TTTCTTTCTT TCCTTTCCTT TTCTTTCCTT 240

TCTTTCCTTT CCTTTCTTTC TTGACAGAGT CTTGCTCTGT CACTCAGGCT GGAGTGCAGT 300

GGCGTGATCT CGNCTCACTG CAACCTCTGT CTCCCAGGTT CAAGCAATTT TCCTGCCTCA 360

GCCTCCCGAG TAGCTGAGAT TACAGGCGCC AGCCACCACA CCCAGCTACT GACCTGCTTT 420

T 421

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 997 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:25:

AAACAGCTGG GAGATATGGT GCCTCAGACC AACCCCATGT TATATGTCAA CCCTGACATA 60

TTGGCAGGCA ACATGAATCC AGACTTCTAG GCTGTCATGC GGGCTCTTTT TTGCCAGTCA 120

TTTCTGATCT CTCTGACATG AGCTGTTTCA TTTATGCTTT GGCTGCCCAG CAAGTATGAT 180

TTGTCCTTTC ACAATTGGTG GCGATGGTTT TCTCCTTCCA TTTATCTTTC TAGGTCATCC 240

CCTTCTAAAT GCCCATCATT AGATGATAGG TGGTACATGC ACAGTTGCTC TGGGAGTCTT 300

CAGAATAGAA ACTACCCATC TCAAGAGGAG CTCATTAAGG TTGTTGATGT GGAGGAGCAA 360

CAGCTGGAAG AGTCTGGGCC ACACGATTTG ACGGAAACAT CTTACTTGCC AAGGCAAGAT 420

CTAGGTAATA TTTCATCTGC TGTATTGGAA CAAACACTYT GATTTTACTC TGAATCCTAC 480

ATAAAGATAT TCTGGTTAAC CAACTTTTAG ATGTACTAGT CTATCATGGA CACTTTTGTT 540

ATACTTAATT AAGCCCACTT TAGAAAAATA GCTCAAGTGT TAATCAAGGT TTACTTGAAA 600

ATTATTGAAA CTGTTAATCC ATCTATATTT TAATTAATGG TTTAACTAAT GATTTTGAGG 660

ATGWGGGAGT CKTGGTGTAC TCTAMATGTA TTATTTCAGG CCAGGCATAG TGGCTCACGC 720

CTGGTAATCC CAGTAYYCMR GAGCCCGAGG CAGGTGGAGC CAGCTGAGGT CAGGAGTTCA 780

-continued

AGACCTGTCT TGGCCAACAT GGGNGAAACC CTGTCTTCTT CTTAAAAAAN ACAAAAAAAA 840

TTAACTGGGT TGTGCTTAGG TGNATGCCCC GNATCCTAGT TNTTCTTGNG GGTTGAGGGA 900

GGAGATCACN TTGGACCCCG GAGGGGNGGG TGGGGGNCAG CAGGNCAAAA CACNGACCCA 960

GCTGGGGTGG AAGGGAAGCC CACTCNAAAA AANNTTN 997

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 639 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:26:

TTTTTAGGAA ACAAGCTACT TTGGATTTCC ACCAACACCT GTATTCATGT ACCCATTTTT 60

CTCTTAACCT AACTTTATTG GTCTTTTTAA TTCTTAACAG AGACCAGAAC TTTGTAATTC 120

AACATTCATC GTTGTGTAAA TTAAACTTCT CCCATTCCTT TCAGAGGGAA CCCCTTACCT 180

GGAATCTGGA ATCAGCCTCT TCTCTGATGA CCCTGAATCT GATCCTTCTG AAGACAGAGC 240

CCCAGAGTCA GCTCGTGTTG GCAACATACC ATCTTCAACC TCTGCATTGA AAGTTCCCCA 300

ATTGAAAGTT GCAGAATCTG CCCAGAGTCC AGCTGCTGCT CATACTACTG ATACTGCTGG 360

GTATAATGCA ATGGAAGAAA GTGTGAGCAG GGAGAAGCCA GAATTGACAG CTTCAACAGA 420

AAGGGTCAAC AAAAGAATGT CCATGGTGGT GTCTGGCCTG ACCCCAGAAG AATTTGTGAG 480

TGTATCCATA TGTATCTCCC TAATGACTAA GACTTAACAA CATTCTGGAA AGAGTTTTAT 540

GTAGGTATTG TCAATTAATA ACCTAGAGGA AGAAATCTAG AAAACAATCA CAGTTCTGTG 600

TAATTTAATT TCGATTACTA ATTTCTGAAA ATTTAGAA Y 639

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 922 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:27:

NCCCNNCCCC CNAATCTGAA ATGGGGGTAA CCCCCCCCCA ACCGANACNT GGGTNGCNTA 60

GAGANTTTAA TGGCCCNTTC TGAGGNACAN AAGCTTAAGC CAGGNGACGT GGANCNATGN 120

GTTGTTTNTT GTTTGGTTAC CTCCAGCCTG GGTGACAGAG CAAGACTCTG TCTAAAAAAA 180

AAAAAAAAAA AAATCGACTT TAAATAGTTC CAGGACACGT GTAGAACGTG CAGGATTGCT 240

ACGTAGGTAA ACATATGCCA TGGTGGGATA ACTAGTATTC TGAGCTGTGT GCTAGAGGTA 300

-continued

ACTCATGATA ATGGAATATT TGATTTAATT TCAGATGCTC GTGTACAAGT TTGCCAGAAA 360

ACACCACATC ACTTTAACTA ATCTAATTAC TGAAGAGACT ACTCATGTTG TTATGAAAAC 420

AGGTATACCA AGAACCTTTA CAGAATACCT TGCATCTGCT GCATAAAACC ACATGAGGCG 480

AGGCACGGTG GCGCATGCCT GTAATCGCAG CACTTTGGGA GGCCGAGGCG GGCAGATCAC 540

GAGATTAGGA GATCGAGACC ATCCTGGCCA GCATGGTGAA ACCCCGTCTC TACTANNAAA 600

TGGNAAAATT ANCTGGGTGT GGTCGCGTGC NCCTGTAGTC CCAGCTACTC GTGAGGCTGA 660

GGCAGGAGAA TCACTTGAAC CGGGGAAATG GAGGTTTCAG TGAGCAGAGA TCATNCCCCT 720

NCATTCCAGC CTGGCGACAG AGCAAGGCTC CGTCNCCNAA AAAATAAAAA AAAACGTGAA 780

CAAATAAGAA TATTTGTTGA GCATAGCATG GATGATAGTC TTCTAATAGT CAATCAATTA 840

CTTTATGAAA GACAAATAAT AGTTTTGCTG CTTCCTTACC TCCTTTTGTT TTGGGTTAAG 900

ATTTGGAGTG TGGGCCAGGC AC 922

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 867 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GATCTATAGC TAGCCTTGGC GTCTAGAAGA TGGGTGTTGA GAAGAGGGAG TGGAAAGATA 60

TTTCCTCTGG TCTTAACTTC ATATCAGCCT CCCCTAGACT TCCAAATATC CATACCTGCT 120

GGTTATAATT AGTGGTGTTT TCAGCCTCTG ATTCTGTCAC CAGGGGTT[illegible] AGAATCATAA 180

ATCCAGATTG ATCTTGGGAG TGTAAAAAAC TGAGGCTCTT TAGCTTCTTA GGACAGCACT 240

TCCTGATTTT GTTTTCAACT TCTAATCCTT TGAGTGTTTT TCATTCTGCA GATGCTGAGT 300

TTGTGTGTGA ACGGACACTG AAATATTTTC TAGGAATTGC GGGAGGAAAA TGGGTAGTTA 360

GCTATTTCTG TAAGTATAAT ACTATTTCTC CCCTCCTCCC TTTAACACCT CAGAATTGCA 420

TTTTTACACC TAACATTTAA CACCTAAGGT TTTTGCTGAT GCTGAGTCTG AGTTACCAAA 480

AGGTCTTTAA ATTGTAATAC TAAACTACTT TTATCTTTAA TATCACTTTG TTCAAGATAA 540

GCTGGTGATG CTGGGAAAAT GGGTCTCTTT TATAACTAAT AGGACCTAAT CTGCTCCTAG 600

CAATGTTAGC ATATGAGCTA GGGATTTATT TAATAGTCGG CAGGAATCCA TGTGCARCAG 660

NCAAACTTAT AATGTTTAAA TTAAACATCA ACTCTGTCTC CAGAAGGAAA CTGCTGCTAC 720

AAGCCTTATT AAAGGGCTGT GGCTTTAGAG GGAAGGACCT CTCCTCTGTC ATTCTTCCTG 780

TGCTCTTTTG TGAATCGCTG ACCTCTCTAT CTCCGTGAAA AGAGCACGTT CTTCTGCTGT 840

ATGTAACCTG TCTTTTCTAT GATCTCT 867

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 361 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```
NAAAAACGGG GNNGGGANTG GGCCTTAAAN CCAAAGGGCN AACTCCCCAA CCATTNAAAA      60

ANTGACNGGG GATTATTAAA ANCGGCGGGA AACATTTCAC NGCCCAACTA ATATTGTTAA     120

ATTAAAACCA CCACCNCTGC NCCAAGGAGG GAAACTGCTG CTACAAGCCT TATTAAAGGG     180

CTGTGGCTTT AGAGGGAAGG ACCTCTCCTC TGTCATTCTT CCTGTGCTCT TTTGTGAATC     240

GCTGACCTCT CTATGTCCGT GAAAAGAGCA CGTTCTTCGT CTGTATGTAA CCTGTCTTTT     300

CTATGATCTC TTTAGGGGTG ACCCAGTCTA TTAAAGAAAG AAAAATGCTG AATGAGGTAA     360

GTACTTGATG TTACAAACTA ACCAGAGATA TTCATTCAGT CATATAGTTA AAAATGTATT     420

TGCTTCCTTC CATCAATGCA CCACTTTCCT TAACAATGCA CAAATTTTCC ATGATAATGA     480

GGATCATCAA GAATTATGCA GGCCTGCACT GTGGCTCATA CCTATAATCC CAGCGCTTTG     540

GGAGGCTGAG GCGCTTGGAT C                                               561
```

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 567 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```
AATTTTTTGT ATTTTTAGTA GAGATGAGGT TCACCATGTT GGTCTAGATC TGGTGTCGAA      60

CGTCCTGACC TCAAGTGATC TGCCAGCCTC AGTCTCCCAA AGTGCTAGGA TTACAGGGGT     120

GAGCCACTGC GCCTGGCCTG AATGCCTAAA ATATGACGTG TCTGCTCCAC TTCCATTGAA     180

GGAAGCTTCT CTTTCTCTTA TCCTGATGGG TTGTGTTTGG TTTCTTTCAG CATGATTTTG     240

AAGTCAGAGG AGATGTGGTC AATGGAAGAA ACCACCAAGG TCCAAAGCGA GCAAGAGAAT     300

CCCAGGACAG AAAGGTAAAG CTCCCTCCCT CAAGTTGACA AAAATCTCAC CCCACCACTC     360

TGTATTCCAC TCCCCTTTGC AGAGATGGGC CGCTTCATTT TGTAAGACTT ATTACATACA     420

TACACAGTGC TAGATACTTT CACACAGGTT CTTTTTTCAC TCTTCCATCC CAACCACATA     480

AATAAGTATT GTCTCTACTT TATGAATGAT AAAACTAAGA GATTTAGAGA GGCTGTGTAA     540

TTTGGATTCC CGTCTCGGGT TCAGATC                                         567
```

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 833 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
TTGGCCTGAT TGGTGACAAA AGTGAGATGC TCAGTCCTTG AATGACAAAG AATGCCTGTA    60

GAGTTGCAGG TCCAACTACA TATGCACTTC AAGAAGATCT TCTGAAATCT AGTAGTGTTC   120

TGGACATTGG ACTGCTTGTC CCTGGGAAGT AGCAGCAGAA ATGATCGGTG GTGAACAGAA   180

GAAAAAGAAA AGCTCTTCCT TTTTGAAAGT CTGTTTTTTG AATAAAAGCC AATATTCTTT   240

TATAACTAGA TTTTCCTTCT CTCCATTCCC CTGTCCCTCT CTCTTCCTCT CTTCTTCCAG   300

ATCTTCAGGG GGCTAGAAAT CTGTTGCTAT GGGCCCTTCA CCAACATGCC CACAGGTAAG   360

AGCCTGGGAG AACCCCAGAG TTCCAGCACC AGCCTTTGTC TTACATAGTG GAGTATTATA   420

AGCAAGGTCC CACGATGGGG GTTCCTCAGA TTGCTGAAAT GTTCTAGAGG CTATTCTATT   480

TCTCTACCAC TCTCCAAACA AAACAGCACC TAAATGTTAT CCTATGGCAA AAAAAAACTA   540

TACCTTGTCC CCCTTCTCAA GAGCATGAAG GTGGTTAATA GTTAGGATTC AGTATGTTAT   600

GTGTTCAGAT GGCGTTGAGC TGCTGTTAGT GCC                                633
```

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 470 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:32:

```
TTTGAGAGAC TATCAAACCT TATACCAAGT GGCCTTATGG AGACTGATAA CCAGAGTACA    60

TGGCATATCA GTGGCAAATT GACTTAAAAT CCATACCCCT ACTATTTTAA GACCATTGTC   120

CTTTGGAGCA GAGAGACAGA CTCTCCCATT GAGAGGTCTT GCTATAAGCC TTCATCCGGA   180

GAGTGTAGGG TAGAGGGCCT GGGTTAAGTA TGCAGATTAC TGCAGTGATT TTACATGTAA   240

ATGTCCATTT TAGATCAACT GGAATGGATG GTACAGCTGT GTGGTGCTTC TGTGGTGAAG   300

GAGCTTTCAT CATTCACCCT TGGCACAGTA AGTATTGGGT GCCCTGTCAG TGTGGGAGGA   360

CACAATATTC TCTCCTGTGA GCAAGACTGG CACCTGTCAG TCCCTATGGA TGCCCCTACT   420

GTAGCCTCAG AAGTCTTCTC TGCCCACATA CCTGTGCCAA AAGACTCCAT              470
```

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 517 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

GGTGGTACGT GTCTGTAGTT CCAGCTACTT GGGAGGCTGA GATGGAAGGA TTGCTTGAGC 60

CCAGGAGGCA GAGGTGGNAN NTTACGCTGA GATCACACCA CTGCACTCCA GCCTGGGTGA 120

CAGAGCAAGA CCCTGTCTCA AAACAAACA AAAAAAATGA TGAAGTGACA GTTCCAGTAG 180

TCCTACTTTG ACACTTTGAA TGCTCTTTCC TTCCTGGGGA TCCAGGGTGT CCACCCAATT 240

GTGGTTGTGC AGCCAGATGC CTGGACAGAG GACAATGGCT TCCATGGTAA GGTGCCTCGC 300

ATGTACCTGT GCTATTAGTG GGGTCCTTGT GCATGGGTTT GGTTTATCAC TCATTACCTG 360

GTGCTTGAGT AGCACAGTTC TTGGCACATT TTTAAATATT TGTTGAATGA ATGGCTAAAA 420

TGTCTTTTTG ATGTTTTTAT TGTTATTTGT TTTATATTGT AAAAGTAATA CATGAACTGT 480

TTCCATGGGG TGGGAGTAAG ATATGAATGT TCATCAC 517

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 434 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

CAGTAATCCT NAGAACTCAT ACGACCGGGC CCCTGGAGTC GNTGNTTNGA GCCTAGTCCN 60

GGAGAATGAA TTGACACTAA TCTCTGCTTG TGTTCTCTGT CTCCAGCAAT TGGGCAGATG 120

TGTGAGGCAC CTGTGGTGAC CCGAGAGTGG GTGTTGGACA GTGTAGCACT CTACCAGTGC 180

CAGGAGCTGG ACACCTACCT GATACCCCAG ATCCCCCACA GCCACTACTG ACTGCAGCCA 240

GCCACAGGTA CAGAGCCACA GGACCCCAAG AATGAGCTTA CAAAGTGGCC TTTCCAGGCC 300

CTGGGAGCTC CTCTCACTCT TCAGTCCTTC TACTGTCCTG GCTACTAAAT ATTTTATGTA 360

CATCAGCCTG AAAAGGACTT CTGGCTATGC AAGGGTCCCT TAAAGATTTT CTGCTTGAAG 420

TCTCCCTTGG AAAT 434

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:35:

GATAAATTAA AACTGCGACT GCGCGGCGTG 30

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GTAGTAGAGT CCCGGGAAAG GGACAGGGGG 30

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:37:

ATATATATAT GTTTTTCTAA TGTGTTAAAG 30

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:38:

GTAAGTCAGC ACAAGAGTGT ATTAATTTGG 30

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

-continued

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:39:

TTTCTTTTTC TCCCCCCCCT ACCCTGCTAG 30

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:40:

GTAAGTTTGA ATGTGTTATG TGGCTCCATT 30

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:41:

AGCTACTTTT TTTTTTTTTT TTTGAGACAG 30

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:42:

GTAAGTGCAC ACCACCATAT CCAGCTAAAT 30

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

-continued

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:43:

AATTGTTCTT TCTTTCTTTA TAATTTATAG 30

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:44:

GTATATAATT TGGTAATGAT GCTAGGTTGG 30

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:45:

GAGTGTGTTT CTCAAACAAT TTAATTTCAG 30

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:46:

CTAAGTGTTG AATATCCCAA GAATGACACT 30

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:47:

AAACATAATG TTTTCCCTTG TATTTTACAG 30

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:48:

GTAAAACCAT TTGTTTTCTT CTTCTTCTTC 30

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:49:

TGCTTGACTG TTCTTTACCA TACTGTTTAG 30

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:50:

GTAAGGGTCT CAGGTTTTTT AAGTATTTAA 30

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

-continued

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:51:

TGATTTATTT TTTGGGGGGA AATTTTTTAG 30

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:52:

GTGAGTCAAA GAGAACCTTT GTCTATGAAG 30

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:53:

TCTTATTAGG ACTCTGTCTT TTCCCTATAG 30

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:54:

GTAATGGCAA AGTTTGCCAA CTTAACAGGC 30

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

-continued

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:55:

GAGTACCTTG TTATTTTTGT ATATTTTCAG 30

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:56:

GTATTGGAAC CAGGTTTTTG TGTTTGCCCC 30

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:57:

ACATCTGAAC CTCTGTTTTT GTTATTTAAG 30

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:58:

AGGTAAAAAG CGTGTGTGTG TGTGCACATG 30

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

-continued

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:59:

CATTTTCTTG GTACCATTTA TCGTTTTTGA 30

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:60:

GTGTGTATTG TTGGCCAAAC ACTGATATCT 30

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:61:

AGTAGATTTG TTTTCTCATT CCATTTAAAG 30

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:62:

GTAAGAAACA TCAATGTAAA GATGCTGTGG 30

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:63:

ATGGTTTTCT CCTTCCATTT ATCTTTCTAG 30

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:64:

GTAATATTTC ATCTGCTGTA TTGGAACAAA 30

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:65:

TGTAAATTAA ACTTCTCCCA TTCCTTTCAG 30

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:66:

GTGAGTGTAT CCATATGTAT CTCCCTAATG 30

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

-continued

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:67:

ATGATAATGG AATATTTGAT TTAATTTCAG 30

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:68:

GTATACCAAG AACCTTTACA GAATACCTTG 30

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:69:

CTAATCCTTT GAGTGTTTTT CATTCTGCAG 30

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:70:

GTAAGTATAA TACTATTTCT CCCCTCCTCC 30

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:71:

TGTAACCTGT CTTTTCTATG ATCTCTTTAG 30

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:72:

GTAAGTACTT GATGTTACAA ACTAACCAGA 30

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:73:

TCCTGATGGG TTGTGTTTGG TTTCTTTCAG 30

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:74:

GTAAAGCTCC CTCCCTCAAG TTGACAAAAA 30

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

-continued

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:75:

CTGTCCCTCT CTCTTCCTCT CTTCTTCCAG 30

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:76:

GTAAGAGCCT GGGAGAACCC CAGAGTTCCA 30

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:77:

AGTGATTTTA CATGTAAATG TCCATTTTAG 30

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:78:

GTAAGTATTG GGTGCCCTGT CAGTGTGGGA 30

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

-continued

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:79:

```
TTGAATGCTC TTTCCTTCCT GGGGATCCAG                                    30
```

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:80:

```
GTAAGGTGCC TCGCATGTAC CTGTGCTATT                                    30
```

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:81:

```
CTAATCTCTG CTTGTGTTCT CTGTCTCCAG                                    30
```

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: peptide

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:82:

```
Cys Pro Ile Cys Leu Gln Leu Ile Lys Glu Pro Val Ser Thr Lys Cys
1               5                   10                  15
Asp His Ile Phe Cys Lys Phe Cys Met Leu Lys Leu Leu Asn Gln Lys
            20                  25                  30
Lys Gly Pro Ser Gln Cys Pro Leu Cys Lys
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

-continued

(i i) MOLECULE TYPE: peptide

(i i i) HYPOTHETICAL: NO

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:83:

```
Cys Pro Ile Cys Leu Glu Leu Leu Lys Glu Pro Val Ser Ala Asp Cys
1               5                   10                  15

Asn His Ser Phe Cys Arg Ala Cys Ile Thr Leu Asn Tyr Glu Ser Asn
            20                  25                  30

Arg Asn Thr Asp Gly Lys Gly Asn Cys Pro Val Cys Arg
        35                  40                  45
```

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 41 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: peptide

(i i i) HYPOTHETICAL: NO

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:84:

```
Cys Pro Ile Cys Leu Asp Met Leu Lys Asn Thr Met Thr Thr Lys Glu
1               5                   10                  15

Cys Leu His Arg Phe Cys Ser Asp Cys Ile Val Thr Ala Leu Arg Ser
            20                  25                  30

Gly Asn Lys Glu Cys Pro Thr Cys Arg
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: peptide

(i i i) HYPOTHETICAL: NO

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:85:

```
Cys Pro Val Cys Leu Gln Tyr Phe Ala Glu Pro Met Met Leu Asp Cys
1               5                   10                  15

Gly His Asn Ile Cys Cys Ala Cys Leu Ala Arg Cys Trp Gly Thr Ala
            20                  25                  30

Cys Thr Asn Val Ser Cys Pro Gln Cys Arg
        35                  40
```

What is claimed is:

1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.

2. The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1.

3. The isolated DNA of claim 1 which contains BRCA1 regulatory sequences.

4. The isolated DNA of claim 2 which contains BRCA1 regulatory sequences.

5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.

6. An isolated DNA having at least 15 nucleotides of the DNA of claim 2.

7. An isolated DNA selected from the group consisting of:

(a) a DNA having the nucleotide sequence set forth in SEQ ID NO:1 having T at nucleotide position 4056;

(b) a DNA having the nucleotide sequence set forth in SEQ ID NO:1 having an extra C at nucleotide position 5385;

(c) a DNA having the nucleotide sequence set forth in SEQ ID NO: 1 having G at nucleotide position 5443; and, (d) a DNA having the nucleotide sequence set forth in SEQ ID NO:1 having 11 base pairs at nucleotide positions 189–199 deleted.

8. A replicative cloning vector which comprises the isolated DNA of claim **1** or parts thereof and a replicon operative in a host cell.

9. A replicative cloning vector which comprises the isolated DNA of claim **2** or parts thereof and a replicon operative in a host cell.

10. An expression system which comprises the isolated DNA of claim **1** or parts thereof operably linked to suitable control sequences.

11. An expression system which comprises the isolated DNA of claim **2** or parts thereof operably linked to suitable control sequences.

12. Host cells transformed with the expression system of claim **10**.

13. Host cells transformed with the expression system of claim 11.

14. A method of producing BRCA1 polypeptide which comprises culturing the cells of claim 12 under conditions effective for the production of saod BRCA1 polypeptide and harvesting the BRCA1 polypeptide.

15. A method of producing BRCA1 polypeptide which comprises culturing the cells of claim 13 under conditions effective for the producton of said BRCA1 polypeptide and harvesting the BRCA1 polypeptide.

16. A pair of single-stranded DNA primers for determination of a nuycleotide sequence of a BRCA1 gene by a polymerase chin reaction, the sequence of said primers being derived from human chromosomne 17q, wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA having all or part of the sequence of the BRCA1 gene.

17. The pair of primers of claim **16** wherein said BRCA1 gene has the nucleotide sequence set forth in SEQ ID NO:1.

18. A kit for detecting mutations in the BRCA1 gene resulting in a susceptibility to breast and ovarians cancers comprising at least one oligonucleotide prime specific for a BRCA1 gene mutation and instructions relatiing to detectiong mutations in the BRCA1 gene.

19. A kit for detecting mutations in the BRCA1 gene resulting in a sisceptibility to breast and ovarian cancers comprising at least one allele-specific oligimucleotide probe for a BRCA1 gene mutation and instructions relating to detecting mutations in the BRCA1 gene.

20. A method for screening potential cancer therapeutics which comprises: growing a transformed eukaryotic host cell containing an altered BRCA1 gene causing cancer in the presence of a compound suspected of being a cancer therapeutic, growing said transformed eukaryotic host cell in the absence of said compound, determining the rate of growth of said host cell in the presence of said compound and the rate of growth of said host cell in the absence of said compound and comparing the growth rate of said host cells, wherein a slower rate of growth of said host cell in the presence of said compound is indicative of a cancer therapeutic.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,747,282 Page 1 of 6
DATED : May 5, 1998
INVENTOR(S) : Mark H. Skolnick et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Please add the following references:
--

U.S. PATENT DOCUMENTS

5,236,844	08/1993	Basset et al.

FOREIGN PATENT DOCUMENTS

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91/09964	07/1991	WO
92/00311	01/1992	WO
92/11874	07/1992	WO
94/00764	01/1994	WO
95/19369	07/1995	WO

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Castilla, L.H. et al. (1994). "Mutations in the BRCA 1 gene in families with early-onset breast and ovarian cancer," *Nature Genetics* 8:87-391.

Friedman, L.S. et al. (1994). "Confirmation of BRCA 1 by analysis of germline mutations linked to breast and ovarian cancer in ten families," *Nature Genetics* 8:399-404.

Goldgar, D.E. et al. (1994). "A Large Kindred With 17q-Linked Breast and Ovarian Cancer: Genetic, Pheotypic, and Genealogical Analysis," *J. Natl. Caner Institute 86*:200-209.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,747,282 Page 2 of 6
DATED : May 5, 1998
INVENTOR(S) : Mark. H. Skolnick et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Stampfer, M.R. et al. (1993). "Culture Systems for Study of Human Mammary Epithelial Cell Proliferation, Differentiation and Transformation," *Cancer Surveys* 18:7-34.

Wooster, R. et al. (1994). "Localization of a Breast Cancer Susceptibility Gene, BRCA2, to Chromosome 13q12-13," *Science* 265:2088-2090.

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CERTIFICATE OF CORRECTION

PATENT NO. : 5,747,282 Page 3 of 6
DATED : May 5, 1998
INVENTOR(S) : Mark. H. Skolnick et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

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CERTIFICATE OF CORRECTION

PATENT NO. : 5,747,282 Page 4 of 6
DATED : May 5, 1998
INVENTOR(S) : Mark. H. Skolnick et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

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CERTIFICATE OF CORRECTION

PATENT NO. : 5,747,282 Page 5 of 6
DATED : May 5, 1998
INVENTOR(S) : Mark. H. Skolnick et al.

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O'Connell, P., et al. (1994). "A Radiation Hybrid Map of the BRCA1 Region," *Am. J. Hum. Genet. 54:*526-534.

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PATENT NO. : 5,747,282
DATED : May 5, 1998
INVENTOR(S) : Mark. H. Skolnick et al.

Page 6 of 6

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Go, R.C.P., et al. (1983). "Genetic Epidemiology of Breast Cancer and Associated Cancers in High-Risk Families. I. Segregation Analysis," *J. Natl. Cancer Inst.* 71:455-461. --;

Column 36,
Line 36, "collaborators" should be -- collaborators' --;

Column 155,
Line 17, "saod" should be -- said --.

Signed and Sealed this

Fourth Day of December, 2001

Attest:

Nicholas P. Godici

NICHOLAS P. GODICI
Attesting Officer *Acting Director of the United States Patent and Trademark Office*

PATENT '473

US005693473A

United States Patent [19]

Shattuck-Eidens et al.

[11] **Patent Number:** 5,693,473

[45] **Date of Patent:** Dec. 2, 1997

[54] **LINKED BREAST AND OVARIAN CANCER SUSCEPTIBILITY GENE**

[75] Inventors: **Donna M. Shattuck-Eidens**, Salt Lake City, Utah; **Jacques Simard**, Quebec; **Francine Durocher**, Ste-Foy, both of Canada; **Mitsuuru Emi**, Tokoyo; **Yusuke Nakamura**, Yokohama, both of Japan

[73] Assignees: **Myriad Genetics, Inc.**, Salt Lake City, Utah; **Centre de Recherche du Chul**, Sainte-Foy, Canada; **Cancer Institute**, Tokyo, Japan

[21] Appl. No.: **480,784**

[22] Filed: **Jun. 7, 1995**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 409,305, Mar. 24, 1995, abandoned, which is a continuation-in-part of Ser. No. 348,824, Nov. 29, 1994, abandoned, which is a continuation-in-part of Ser. No. 308,104, Sep. 9, 1994, abandoned, which is a continuation-in-part of Ser. No. 300,266, Sep. 2, 1994, abandoned, which is a continuation-in-part of Ser. No. 289,221, Aug. 12, 1994, abandoned.

[51] **Int. Cl.**^{6} **C12Q 1/68**; C12P 19/34; C07H 21/04; C07H 21/02

[52] **U.S. Cl.** **435/6**; 435/91.2; 536/23.1; 536/24.3; 536/24.33

[58] **Field of Search** 435/6, 91.2; 536/23.1, 536/24.3, 24.33

[56] **References Cited**

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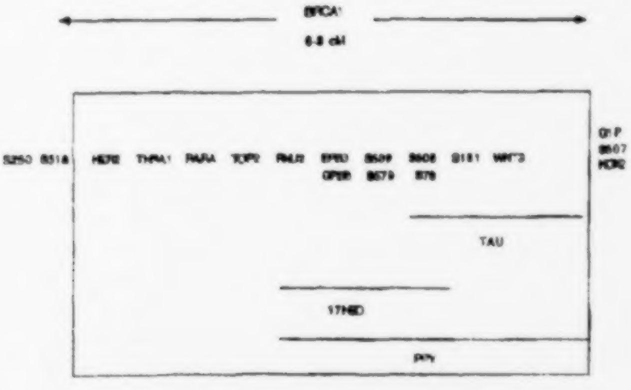
(List continued on next page.)

Primary Examiner—W. Gary Jones
Assistant Examiner—Dianne Rees
Attorney, Agent, or Firm—Venable, Baetjer, Howard & Civiletti, LLP

[57] **ABSTRACT**

The present invention relates generally to the field of human genetics. Specifically, the present invention relates to methods and materials used to isolate and detect a human breast and ovarian cancer predisposing gene (BRCA1), some mutant alleles of which cause susceptibility to cancer, in particular breast and ovarian cancer. More specifically, the invention relates to germline mutations in the BRCA1 gene and their use in the diagnosis of predisposition to breast and ovarian cancer. The present invention further relates to somatic mutations in the BRCA1 gene in human breast and ovarian cancer and their use in the diagnosis and prognosis of human breast and ovarian cancer. Additionally, the invention relates to somatic mutations in the BRCA1 gene in other human cancers and their use in the diagnosis and prognosis of human cancers. The invention also relates to the therapy of human cancers which have a mutation in the BRCA1 gene, including gene therapy, protein replacement therapy and protein mimetics. The invention further relates to the screening of drugs for cancer therapy. Finally, the invention relates to the screening of the BRCA1 gene for mutations, which are useful for diagnosing the predisposition to breast and ovarian cancer.

14 Claims, 18 Drawing Sheets



Map of the early onset breast and ovarian cancer region (BRCA1)

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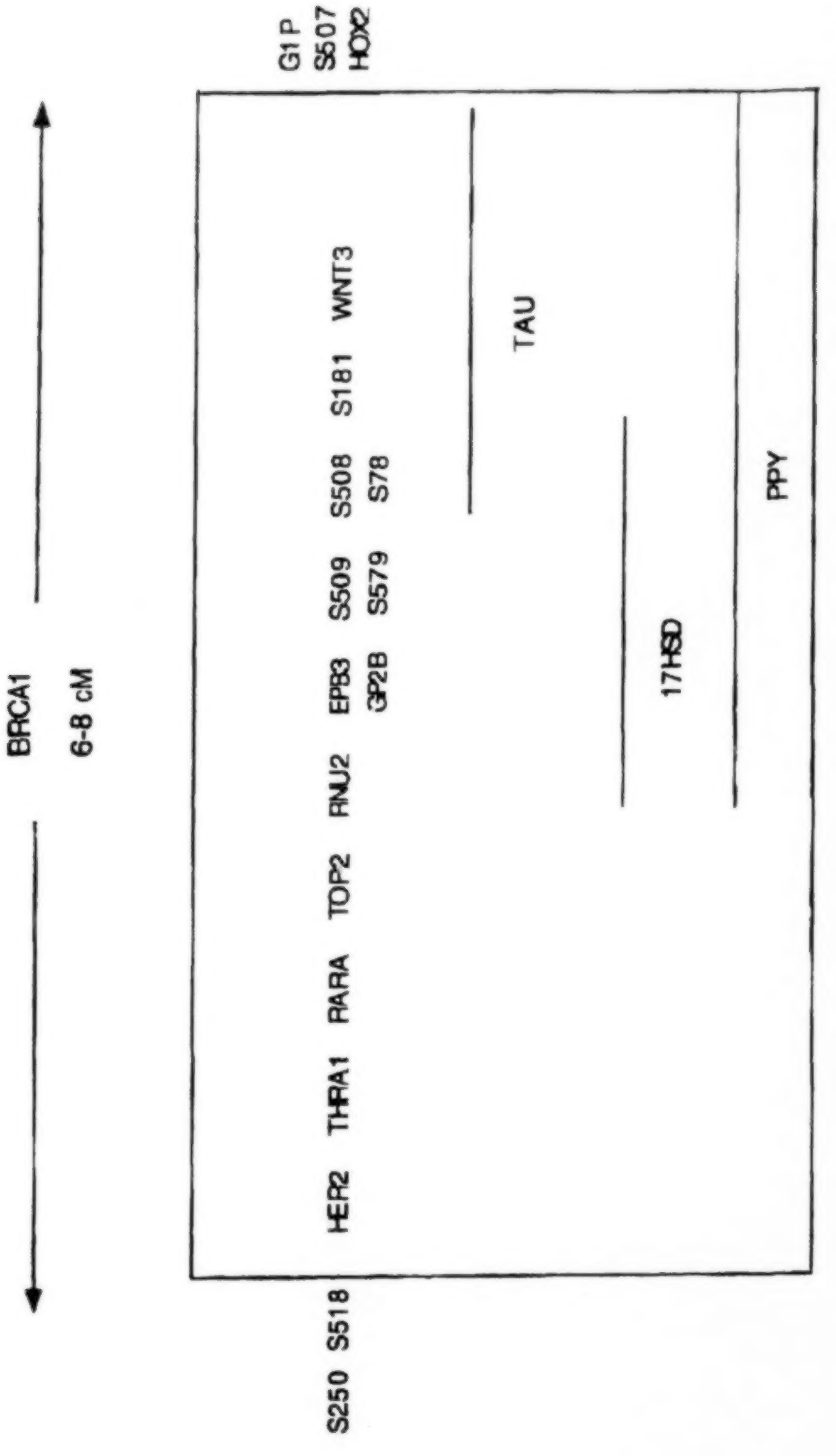
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S508
S78
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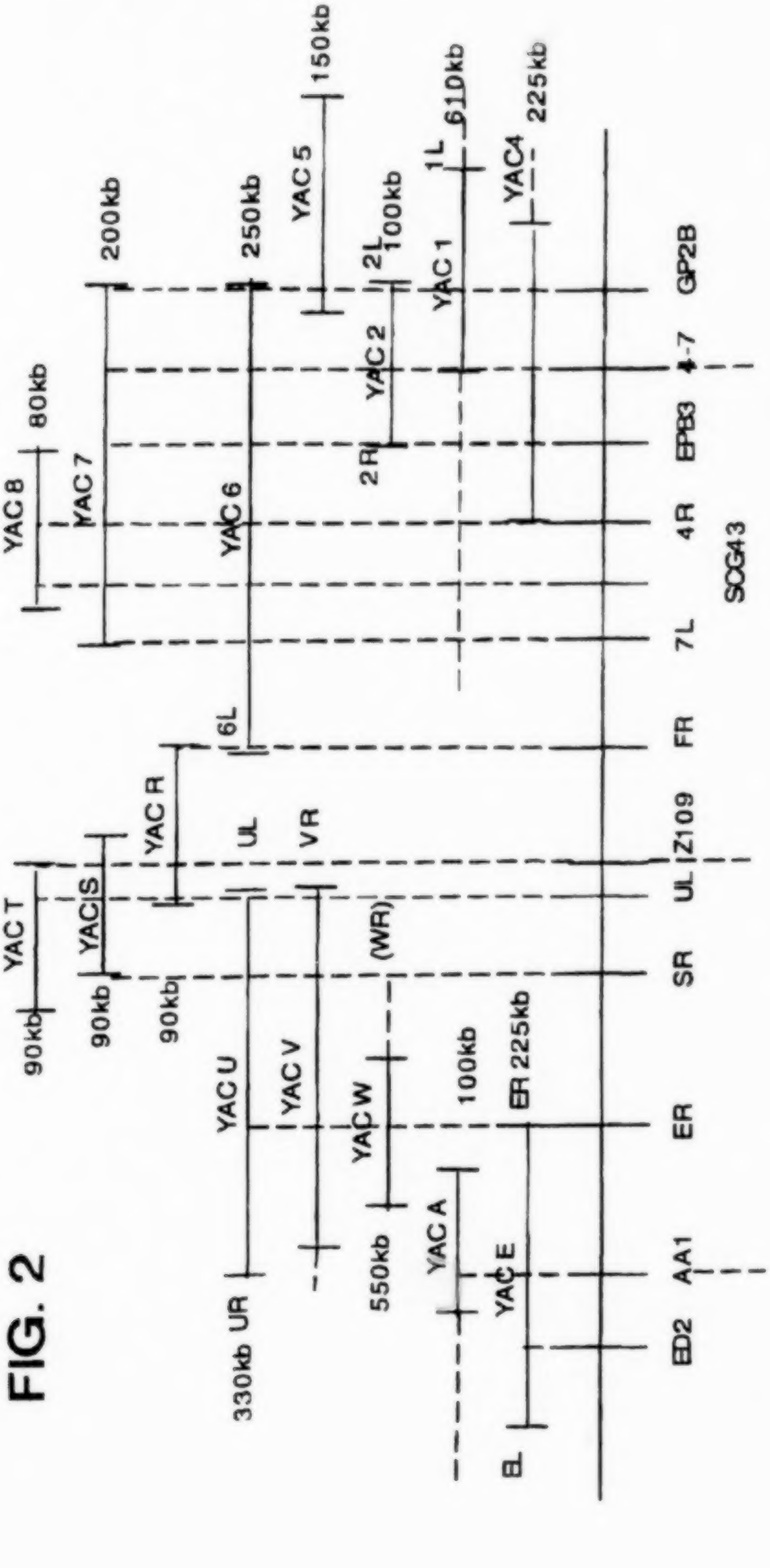
HOX2
TAU
17HSD
PPY

Map of the early onset breast and ovarian cancer region (BRCA1)

FIG. 1

FIG. 2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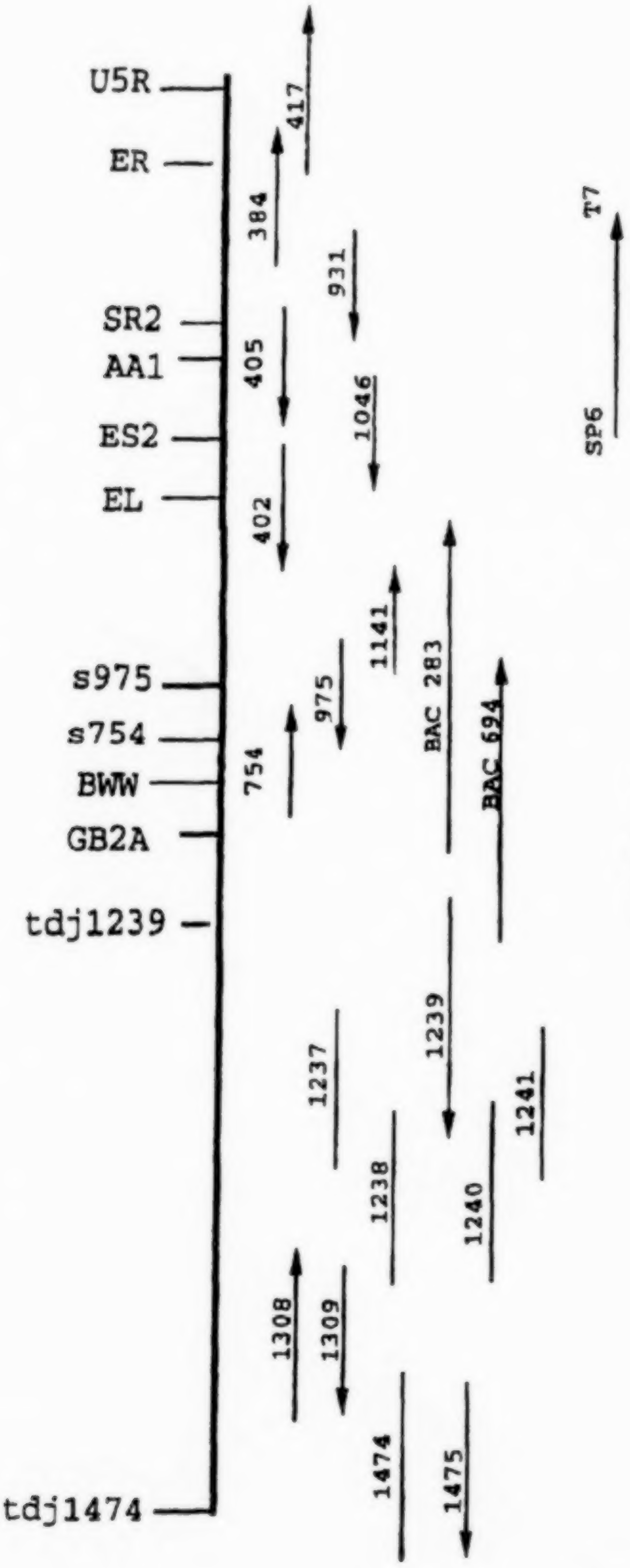
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405
1046
402
1141
975
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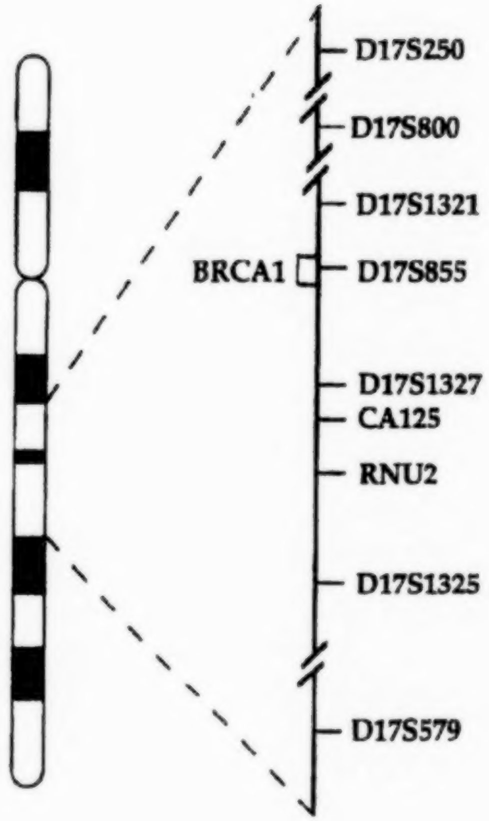
1475

FIG. 3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D17S1321
BRCA1
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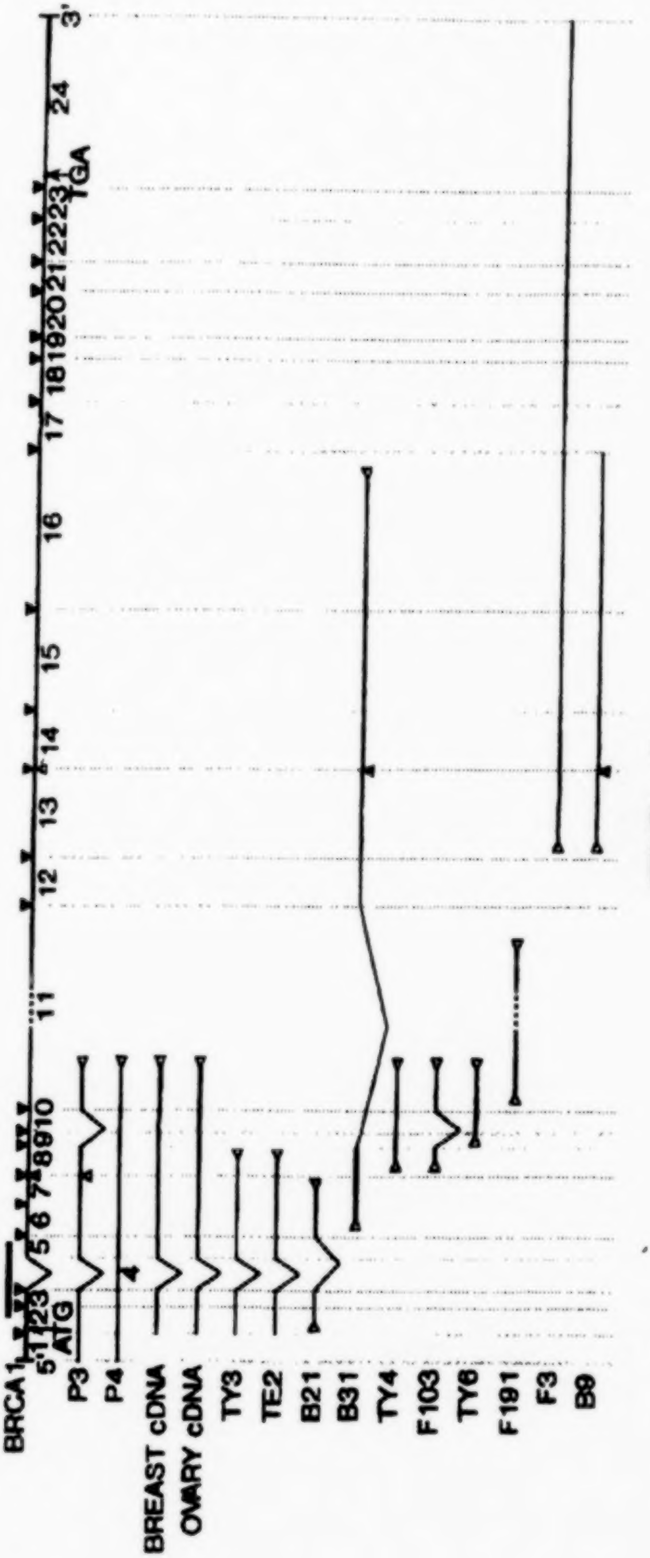
D17S1327
CA125
RNU2
D17S1325
D17S579

FIG. 4

SEQ. ID NO:		
82	BRCA1	CPICLELIKEPVSTK-CDHIFCKFCMLKLLNQKK---GPSQCPLCK
83	RPT1	CPICLELLKEPVSAD-CNHSFCRACITLNYESNRNTDGKGNCPVCR
84	RIN1	CPICLDMLKNTMTTKECLHRFCSDCIVTALRS-----GNKECPTCR
85	RFP1	CPVCLQYFAEPMMLD-CGHNICCACLARCWGTAC---TNVSCPQCR
	C3HC4 motif	C--C------------C-H--C--C----------------C--C

FIG. 5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TGA
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P4
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TE2
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B31
TY4
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F191
F3
B9

FIG. 6

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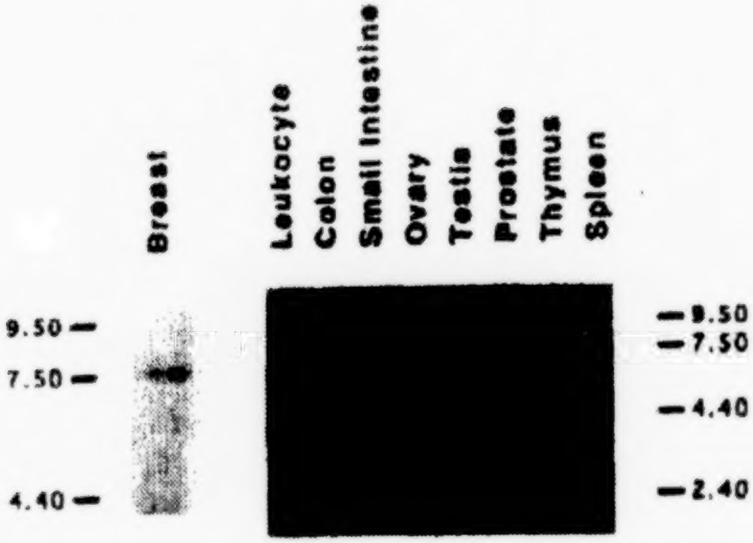
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Colon
Small Intestine
Ovary
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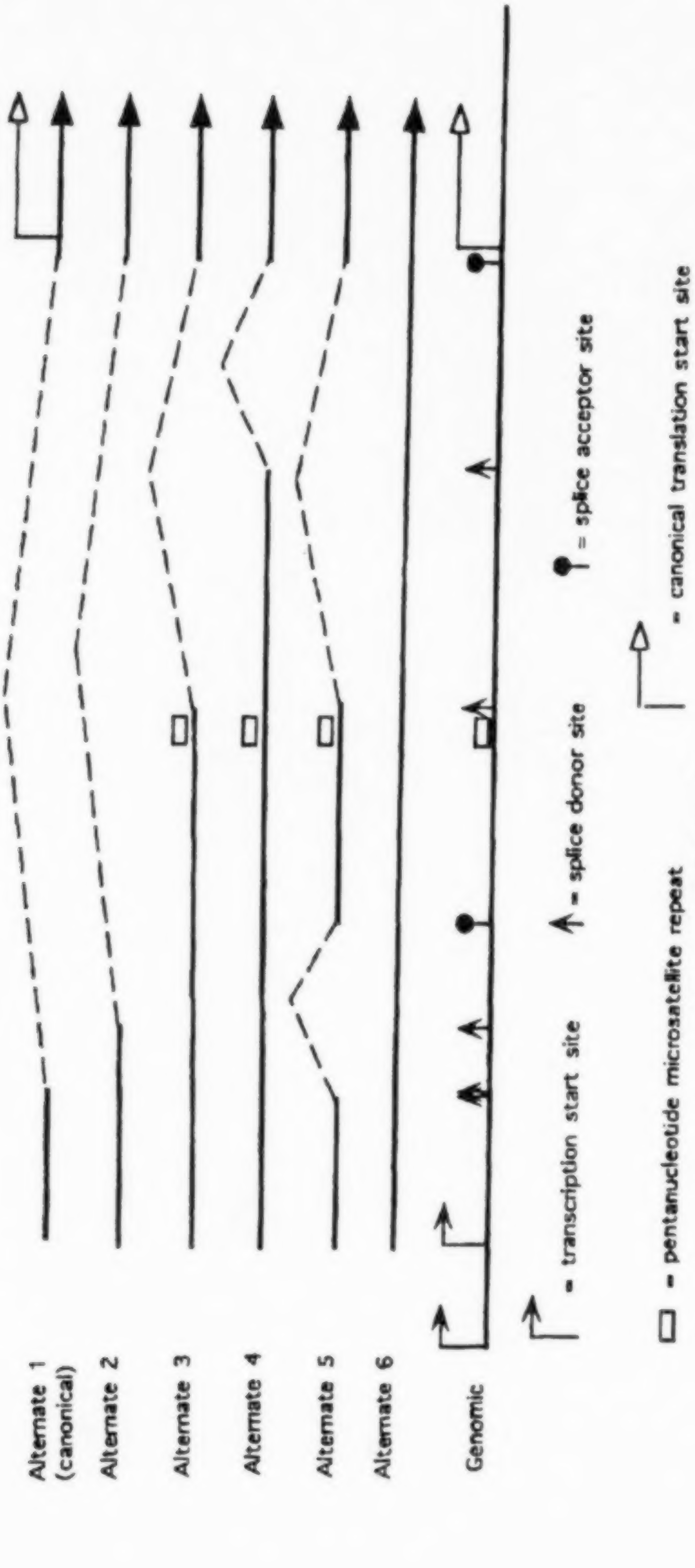
7.50
4.40
2.40

FIG. 7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Alternate 2
Alternate 3
Alternate 4
Alternate 5
Alternate 6
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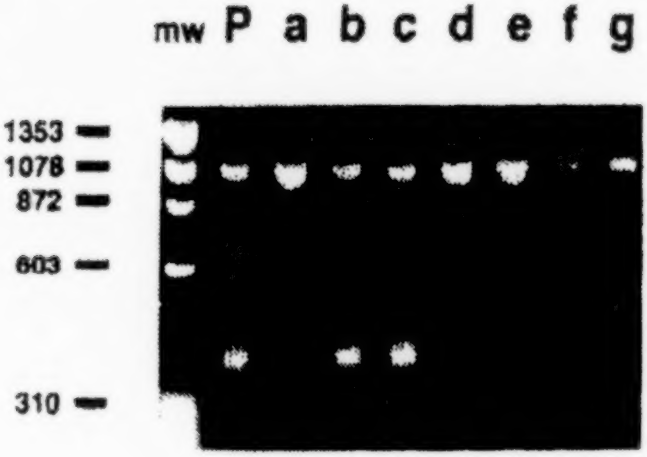
- splice donor site
= splice acceptor site
- pentanucleotide microsatellite repeat
- canonical translation start site

FIG. 8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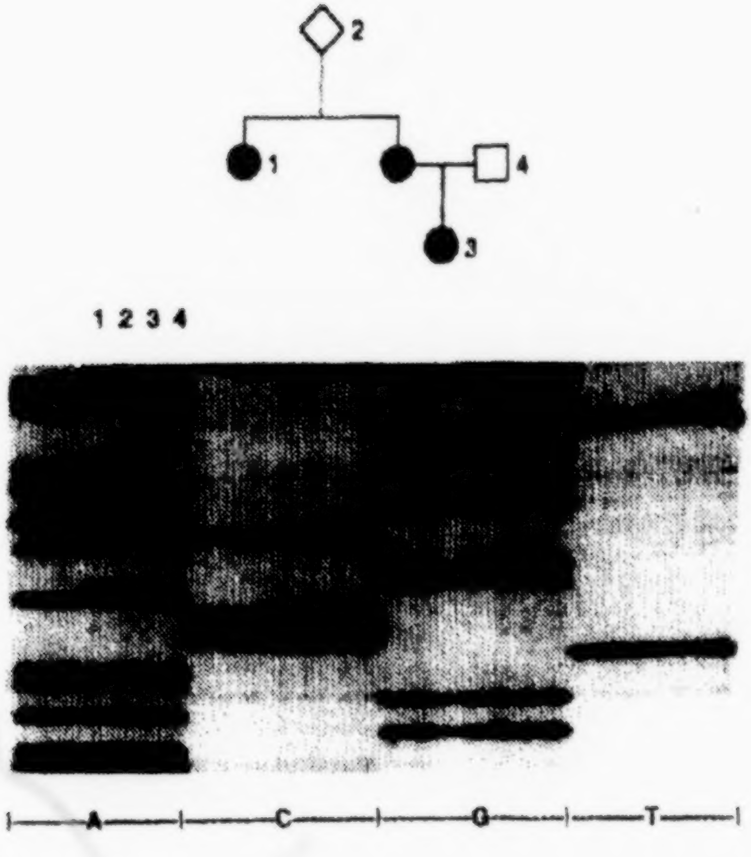
310

FIG. 9A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A
C
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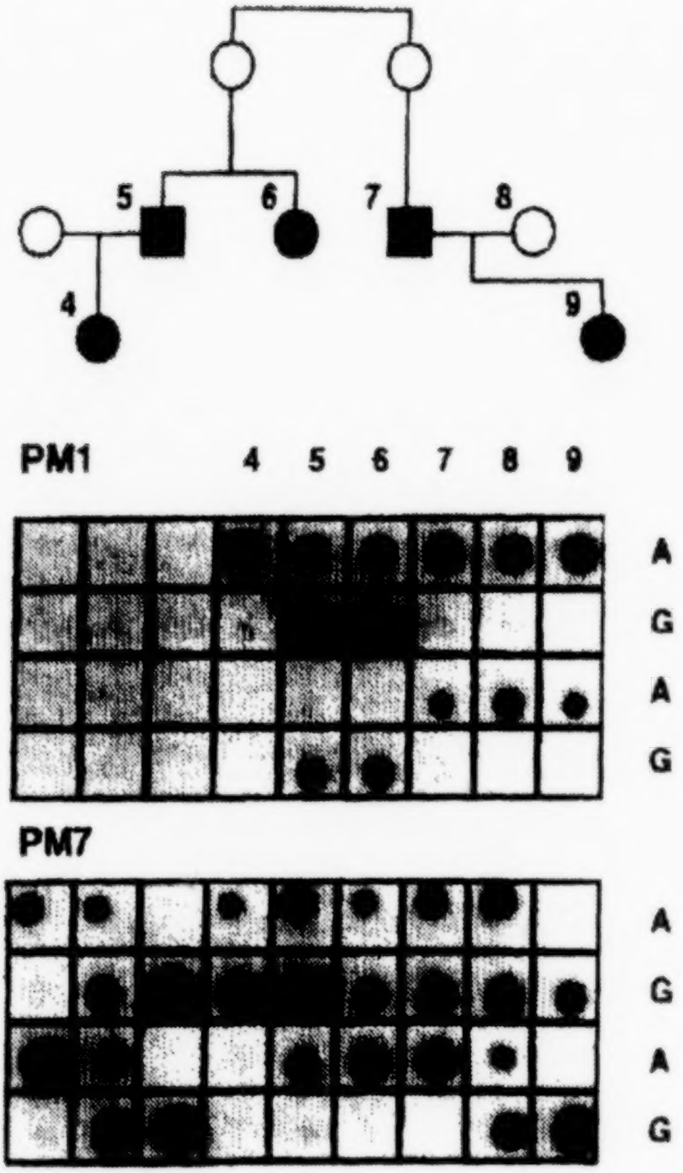
T

FIG. 9B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A
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A
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PM7
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G
A
G

FIG. 9C

```
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2881  ttaacccgtctgcccacctaggcatcccaaagtgctaggattacaggtgtgagtcatcat
2941  gcctggccagtattttagttagctctgtcttttcaagtcatatacaagttcattttcttt
3001  taagtttagttaacaaccttatatcatgtattcttttctagcataaagaaagattcgagg
```

FIG. 10A

```
3061  ccvvvvvvvvvvvvvvtgtgatcataacagtaagccatatgcatgtaagttcagttttcat
3121  agatcattgcttatgtagtttaggttttgcttatgcagcatccaaaaacaattaggaaa
3181  ctattgcttgtaattcacctgccattactttttaaatggctcttaagggcagttgtgaga
3241  ttatcttttcatggctatttgccttttgagtattctttctacaaaaggaagtaaattaaa
3301  ttgttctttctttctttataatttatagATTTTGCATGCTGAAACTTCTCAACCAGAAGA
3361  AAGGGCCTTCACAGTGTCCTTTATGTAAGAATGATATAACCAAAAGgtatataatttggt
3421  aatgatgctaggttggaagcaaccacagtaggaaaaagtagaaattatttaataacatag
3481  cgttcctataaaaccattcatcagaaaatttataaaagagtttttagcacacagtaaat
3541  tatttccaaagttattttcctgaaagttttatgggcatctgccttatacaggtattgvvv
3601  vvvvvvvvvvggtaggcttaaatgaatgacaaaaagttactaaatcactgccatcacacg
3661  gtttatacagatgtcaatgatgtattgattatagaggttttctactgttgctgcatctta
3721  tttttatttgtttacatgtcttttcttattttagtgtccttaaaaggttgataatcactt
3781  gctgagtgtgtttctcaaacaatttaatttcagGAGCCTACAAGAAAGTACGAGATTTAG
3841  TCAACTTGTTGAAGAGCTATTGAAAATCATTTGTGCTTTTCAGCTTGACACAGGTTTGGA
3901  GTgtaagtgttgaatatcccaagaatgacactcaagtgctgtccatgaaaactcaggaag
3961  tttgcacaattactttctatgacgtggtgataagacctttagtctaggttaattttagt
4021  tctgtatctgtaatctattttaaaaaattactcccactggtctcacaccttatttvvvvv
4081  vvvvvvvvaaaaaatcacaggtaaccttaatgcattgtcttaacacaacaaagagcatac
4141  atagggtttctcttggtttctttgattataattcatacatttttctctaactgcaaacat
4201  aatgttttcccttgtattttacagATGCAAACAGCTATAATTTTGCAAAAAAGGAAAATA
4261  ACTCTCCTGAACATCTAAAAGATGAAGTTTCTATCATCCAAAGTATGGGCTACAGAAACC
4321  GTGCCAAAAGACTTCTACAGAGTGAACCCGAAAATCCTTCCTTGgtaaaaccatttgttt
4381  tcttcttcttcttcttcttcttttcttttttttttcttttttttttttgagatggagtctt
4441  gctctgtggcccaggctagaagcagtcctcctgccttagccnccttagtagctgggatta
4501  caggcacgcgcaccatgccaggctaattttttgtatttttagtagagacggggtttcatca
4561  tgttggccaggctggtctcgaactcctaacctcaggtgatcvvvvvvvvvvvvvvvatgatg
4621  gagatcttaaaaagtaatcattctggggctgggcgtagtagcttgcacctgtaatcccag
4681  cacttcgggaggctgaggcaggcagataatttgaggtcaggagtttgagaccagcctggc
4741  caacatggtgaaacccatctctactaaaaatacaaaaattagctgggtgtggtggcacgt
4801  acctgtaatcccagctactcgggaggcggaggcacaagaattgcttgaacctaggacgcg
4861  gaggttgcagcgagccaagatcgcgccactgcactccagcctgggccgtagagtgagact
4921  ctgtctcaaaaaagaaaaaaaagtaattgttctagctgggcgcagtggctcttgcctgta
4981  atcccagcactttgggaggccaaggcgggtggatctcgagtcctagagttcaagaccagc
5041  ctaggcaatgtggtgaaaccccatcgctacaaaaaatacaaaaattagccaggcatggtg
5101  gcgtgcgcatgtagtcccagctccttgggaggctgaggtgggaggatcacttgaacccag
5161  gagacagaggttgcagtgaaccgagatcacgccaccacgctccagcctgggcaacagaac
5221  aagactctgtctaaaaaaatacaaataaaataaaagtagttctcacagtaccagcattca
5281  tttttcaaaagatatagagctaaaaaggaaggaaaaaaaaagtaatgttgggcttttaaa
5341  tactcgttcctatactaaatgttcttaggagtgctggggttttattgtcatcatttatcc
5401  tttttaaaaatgttattggccaggcacggtggctcatggctgtaatcccagcactttggg
5461  aggccgaggcaggcagatcacctgaggtcaggagtgtgagaccagcctggccaacatggc
5521  gaaacctgtctctactaaaaatacaaaaattaactaggcgtggtggtgtacgcctgtagt
5581  cccagctactcgggaggctgaggcaggagaatcaactgaaccagggaggtggaggttgca
5641  gtgtgccgagatcacgccactgcactctagcctggcaacagagcaagattctgtctcaaa
5701  aaaaaaaaacatatatacacatatatcccaaagtgctgggattacatatatatatatata
5761  tatatattatatatatatatatatatatatgtgatatatatgtgatatatatatataacata
5821  tatatatgtaatatatatgtgatatatatataatatatatatgtaatatatatgtgatat
5881  atatatatacacacacacacacatatatatgtatgtgtgtacacacacacacacaaat
5941  tagccaggcatagttgcacacgcttggtagacccagctactcaggaggctgagggaggag
6001  aatctcttgaacttaggaggcggaggttgcagtgagctgagattgcgccactgcactcca
6061  gcctgggtgacagagcaggactctgtacaccccccaaaacaaaaaaaaaagttatcagat
```

FIG. 10B

```
6121  gtgattggaatgtatatcaagtatcagcttcaaaatatgctatattaatacttcaaaaat
6181  tacacaaataatacataatcaggtttgaaaaatttaagacaacmwaaraaaaaawycmaa
6241  tcacamatatcccacacattttattattmctmctmcwattatttgwagagmctgggtct
6300  cacycykttgctwatgctggtctttgaacyccykgccycaarcartcctsctccabcctc
6361  ccaargtgctggggatwataggcatgarctaaccgcacccagccccagacattttagtgt
6421  gtaaattcctgggcattttttcaaggcatcatacatgttagctgactgatgatggtcaat
6481  ttattttgtccatggtgtcaagtttctcttcaggaggaaaagcacagaactggccaagaa
6541  ttgcttgactgttctttaccatactgtttagCAGGAAACCAGTCTCAGTGTCCAACTCTC
6601  TAACCTTGGAACTGTGAGAACTCTGAGGACAAAGCAGCGGATACAACCTCAAAAGACGTC
6661  TGTCTACATTGAATTGGgtaagggtctcaggttttttaagtatttaataataattgctgg
6721  attccttatcttatagttttgccaaaaatcttggtcataatttgtatttgtggtaggcag
6781  ctttgggaagtgaattttatgagccctatggtgagttataaagaatgtaaaagacgcagt
6841  tcccaccttgaagaatcttactttaaaaagggagcaaaagaggccaggcatggtggctca
6901  cacctgtaatcccagcactttgggaggccaaagtgggtggatcacctgaggtcgggagtt
6961  cgagaccagcctagccaacatggagaaactctgtctgtaccaaaaaataaaaaattagcc
7021  aggtgtggtggcacataactgtaatcccagctactcgggaggctgaggcaggagaatcac
7081  ttgaacccgggaggtggaggttgcggtgaaccgagatcgcaccattgcactccagcctgg
7141  gcaaaaatagcgaaactccatctaaaaaaaaaaaagagagcaaaagaaagamtmtctggt
7201  tttaamtmtgtgtaaatatgtttttggaaagatggagagtagcaataagaaaaaacatga
7261  tggattgctacagtatttagttccaagataaattgtactagatgaggaagccttttaaga
7321  agagctgaattgccaggcgcagtggctcacgcctgtaatcccagcactttgggaggccga
7381  ggtgggcggatcacctgaggtcgggagttcaagaccagcctgaccaacatggagaaaccc
7441  catctctactaaaaaaaaaaaaaaaaaaattagccggggtggtggcttatgcctgtaatc
7501  ccagctactcaggaggctgaggcaggagaatcgcttgaacccaggaagcagaggttgcag
7561  tgagccaagatcgcaccattgcactccagcctaggcaacaagagtgaaactccatctcaa
7621  aaaaaaaaaaaaagagctgaatcttggctgggcaggatggctcgtgcctgtaatcctaac
7681  gctttggaagaccgaggcagaaggattggttgagtccacgagtttaagaccagcctggcc
7741  aacataggggaaccctgtctctatttttaaaataataatacatttttggccggtgcggtg
7801  gctcatgcctgtaatcccaatactttgggaggctgaggcaggtagatcacctgaggtcag
7861  agttcgagaccagcctggataacctggtgaaacccctctttactaaaaatacaaaaaaaa
7921  aaaaaaattagctgggtgtggtagcacatgcttgtaatcccagctacttgggaggctgag
7981  gcaggagaatcgcttgaaccagggaggcggaggttacaatgagccaacactacaccactg
8041  cactccagcctgggcaatagagtgagactgcatctcaaaaaaataataatttttaaaaat
8101  aataaatttttttaagcttataaaaagaaaagttgaggccagcatagtagctcacatctg
8161  taatctcagcagtggcagaggattgcttgaagccaggagtttgagaccagcctgggcaac
8221  atagcaagacctcatctctacaaaaaaaatttctttttaaattagctgggtgtggtggtg
8281  tgcatctgtagtcccagctactcaggaggcagaggtgagtggatacattgaacccaggag
8341  tttgaggctgtagtgagctatgatcatgccactgcactccaacctgggtgacagagcaag
8401  acctccaaaaaaaaaaaaaaaagagctgctgagctcagaattcaaactgggctctcaaat
8461  tggattttcttttagaatatatttataattaaaaaggatagccatcttttgagctcccag
8521  gcaccaccatctatttatcataacacttactgttttccccccttatgatcataaattcct
8581  agacaacaggcattgtaaaaatagttatagtagttgatatttaggagcacttaactatat
8641  tccaggcactattgtgcttttcttgtataactcattagatgcttgtcagacctctgagat
8701  tgttcctattatacttattttacagatgagaaaattaaggcacagagaagttatgaaatt
8761  tttccaaggtattaaacctagtaagtggctgagccatgattcaaacctaggaagttagat
8821  gtcagagcctgtgctttttttttgtttttgtttttgttttcagtagaaacgggggtctca
8881  ctttgttggccaggctggtcttgaactcctaacctcaaataatccacccatctcggcctc
8941  ctcaagtgctgggattacaggtgagagccactgtgcctggcgaagcccatgcctttaacc
9001  acttctctgtattacatactagcttaactagcattgtacctgccacagtagatgctcagt
9061  aaatatttctagttgaatatctgtttttcaacaagtacatttttttaacccttttaatta
9121  agaaaactttattgatttatttttgggggaaatttttagGATCTGATTCTTCTGAA
```

FIG. 10C

```
9181   GATACCGTTAATAAGGCAACTTATTGCAGgtgagtcaaagagaacctttgtctatgaagc
9241   tggtattttcctatttagttaatattaaggattgatgtttctctctttttaaaaatattt
9301   taacttttattttaggttcagggatgtatgtgcagtttgttatataggtaaacacacgac
9361   ttgggatttggtgtatagatttttttcatcatccgggtactaagcataccccacagtttt
9421   ttgtttgctttctttctgaatttctccctcttcccaccttcctccctcaagtaggctggt
9481   gtttctccagactagaatcatggtattggaagaaaccttagagatcatctagtttagttc
9541   tctcattttatagtggaggaaatacccttttttgtttgttggatttagttattagcactgt
9601   ccaaaggaatttaggataacagtagaactctgcacatgcttgcttctagcagattgttct
9661   ctaagttcctcatatacagtaatattgacacagcagtaattgtgactgatgaaaatgttc
9721   aaggacttcattttcaactctttctttcctctgttccttatttccacatatctctcaagc
9781   tttgtctgtatgttatataataaactacaagcaaccccaactatgttacctaccttcctt
9841   aggaattattgcttgacccaggtttttttttttttttttttggagacggggtcttgccct
9901   gttgccaggatggagtgtagtggcgccatctcggctcactgcaatctccaactccctggt
9961   tcaagcgattctcctgtctcaatctcacgagtagctgggactacaggtatacaccaccac
10021  gcccggttaattgaccattccatttctttctttccctcttttttttttttttttttgaga
10081  cagagtcttgctctgttgcccaggctggagtacagaggtgtgatctcacctctccgcaac
10141  gtctgcctcccaggttgaagccatactcctgcctcagcctctctagtagctgggactaca
10201  ggcgcgcgccaccacacccggctaatttttgtatttttagtagagatggggtttcaccat
10261  gttggccaggctggtcttgaactcatgacctcaagtggtccacccgcctcagcctcccaa
10321  agtgctggaattacaggcttgagccaccgtgcccagcaaccatttcatttcaactagaag
10381  tttctaaaggagagagcagctttcactaactaaataagattggtcagctttctgtaatcg
10441  aaagagctaaaatgtttgatcttggtcatttgacagttctgcatacatgtaactagtgtt
10501  tcttattaggactctgtcttttccctatagTGTGGAGATCAAGAATTGTTACAAATCAC
10561  CCCTCAAGGAACCAGGGATGAAATCAGTTTGGATTCTGCAAAAAAGGgtaatggcaaagt
10621  ttgccaacttaacaggcactgaaaagagagtgggtagatacagtactgtaattagattat
10681  tctgaagaccatttgggacctttacaacccacaaaatctcttggcagagttagagtatca
10741  ttctctgtcaaatgtcgtggtatggtctgatagatttaaatggtactagactaatgtacc
10801  tataataagaccttcttgtaactgattgttgccctttcgcttttttttttgtttgtttgt
10861  ttgtttttttttgagatggggtctcactctgttgcccaggctggagtgcagtgatgcaat
10921  cttggctcactgcaacctccacctccaaaggctcaagctatcctcccacttcagcctcct
10981  gagtagctgggactacaggcgcatgccaccacacccggttaatttttgtggttttatag
11041  agatggggtttcaccatgttaccgaggctggtctcaaactcctggactcaagcagtctgc
11101  ccacttcagcctcccaaagtgctgcagttacaggcttgagccactgtgcctggcctgccc
11161  tttactttaattggtgtatttgtgtttcatcttttacctactggtttttaaatataggg
11221  agtggtaagtctgtagatagaacagagtattaagtagacttaatggccagtaatctttag
11281  agtacatcagaaccagttttctgatggccaatctgcttttaattcactcttagacgttag
11341  agaaataggtgtggtttctgcatagggaaaattctgaaattaavvvvvvvvvvvvvgatc
11401  ctaagtggaaataatctaggtaaataggaattaaatgaaagagtatgagctacatcttca
11461  gtatacttggtagtttatgaggttagtttctctaatatagccagttggttgatttccacc
11521  tccaaggtgtatgaagtatgtatttttttaatgacaattcagtttttgagtaccttgtta
11581  tttttgtatattttcagCTGCTTGTGAATTTTCTGAGACGGATGTAACAAATACTGAACA
11641  TCATCAACCCAGTAATAATGATTTGAACACCACTGAGAAGCGTGCAGCTGAGAGGCATCC
11701  AGAAAAGTATCAGGGTAGTTCTGTTTCAAACTTGCATGTGGAGCCATGTGGCACAAATAC
11761  TCATGCCAGCTCATTACAGCATGAGAACAGCAGTTTATTACTCACTAAAGACAGAATGAA
11821  TGTAGAAAAGGCTGAATTCTGTAATAAAAGCAAACAGCCTGGCTTAGCAAGGAGCCAACA
11881  TAACAGATGGGCTGGAAGTAAGGAAACATGTAATGATAGGCGGACTCCCAGCACAGAAAA
11941  AAAGGTAGATCTGAATGCTGATCCCCTGTGTGAGAGAAAAGAATGGAATAAGCAGAAACT
12001  GCCATGCTCAGAGAATCCTAGAGATACTGAAGATGTTCCTTGGATAACACTAAATAGCAG
12061  CATTCAGAAAGTTAATGAGTGGTTTTCCAGAAGTGATGAACTGTTAGGTTCTGATGACTC
12121  ACATGATGGGGAGTCTGAATCAAATGCCAAAGTAGCTGATGTATTGGACGTTCTAAATGA
12181  GGTAGATGAATATTCTGGTTCTTCAGAGAAAATAGACTTACTGGCCAGTGATCCTCATGA
```

FIG. 10D

```
12241   GGCTTTAATATGTAAAAGTGAAAGAGTTCACTCCAAATCAGTAGAGAGTAATATTGAAGG
12301   CCAAATATTTGGGAAAACCTATCGGAAGAAGGCAAGCCTCCCCAACTTAAGCCATGTAAC
12361   TGAAAATCTAATTATAGGAGCATTTGTTACTGAGCCACAGATAATACAAGAGCGTCCCCT
12421   CACAAATAAATTAAAGCGTAAAAGGAGACCTACATCAGGCCTTCATCCTGAGGATTTTAT
12481   CAAGAAAGCAGATTTGGCAGTTCAAAAGACTCCTGAAATGATAAATCAGGGAACTAACCA
12541   AACGGAGCAGAATGGTCAAGTGATGAATATTACTAATAGTGGTCATGAGAATAAAACAAA
12601   AGGTGATTCTATTCAGAATGAGAAAAATCCTAACCCAATAGAATCACTCGAAAAAGAATC
12661   TGCTTTCAAAACGAAAGCTGAACCTATAAGCAGCAGTATAAGCAATATGGAACTCGAATT
12721   AAATATCCACAATTCAAAAGCACCTAAAAAGAATAGGCTGAGGAGGAAGTCTTCTACCAG
12781   GCATATTCATGCGCTTGAACTAGTAGTCAGTAGAAATCTAAGCCCACCTAATTGTACTGA
12841   ATTGCAAATTGATAGTTGTTCTAGCAGTGAAGAGATAAAGAAAAAAAAGTACAACCAAAT
12901   GCCAGTCAGGCACAGCAGAAACCTACAACTCATGGAAGGTAAAGAACCTGCAACTGGAGC
12961   CAAGAAGAGTAACAAGCCAAATGAACAGACAAGTAAAAGACATGACAGCGATACTTTCCC
13021   AGAGCTGAAGTTAACAAATGCACCTGGTTCTTTTACTAAGTGTTCAAATACCAGTGAACT
13081   TAAAGAATTTGTCAATCCTAGCCTTCCAAGAGAAGAAAAAGAAGAGAAACTAGAAACAGT
13141   TAAAGTGTCTAATAATGCTGAAGACCCCAAAGATCTCATGTTAAGTGGAGAAAGGGTTTT
13201   GCAAACTGAAAGATCTGTAGAGAGTAGCAGTATTTCATTGGTACCTGGTACTGATTATGG
13261   CAGTCAGGAAAGTATCTCGTTACTGGAAGTTAGCACTCTAGGGAAGGCAAAAACAGAACC
13321   AAATAAATGTGTGAGTCAGTGTGCAGCATTTGAAAACCCCAAGGGACTAATTCATGGTTG
13381   TTCCAAAGATAATAGAAATGACACAGAAGGCTTTAAGTATCCATTGGGACATGAAGTTAA
13441   CCACAGTCGGGAAACAAGCATAGAAATGGAAGAAAGTGAACTTGATGCTCAGTATTTGCA
13501   GAATACATTCAAGGTTTCAAAGCGCCAGTCATTTGCTCCGTTTTCAAATCCAGGAAATGC
13561   AGAAGAGGAATGTGCAACATTCTCTGCCCACTCTGGGTCCTTAAAGAAACAAAGTCCAAA
13621   AGTCACTTTTGAATGTGAACAAAAGGAAGAAAATCAAGGAAAGAATGAGTCTAATATCAA
13681   GCCTGTACAGACAGTTAATATCACTGCAGGCTTTCCTGTGGTTGGTCAGAAAGATAAGCC
13741   AGTTGATAATGCCAAATGTAGTATCAAAGGAGGCTCTAGGTTTTGTCTATCATCTCAGTT
13801   CAGAGGCAACGAAACTGGACTCATTACTCCAAATAAACATGGACTTTTACAAAACCCATA
13861   TCGTATACCACCACTTTTTCCCATCAAGTCATTTGTTAAAACTAAATGTAAGAAAAATCT
13921   GCTAGAGGAAAACTTTGAGGAACATTCAATGTCACCTGAAAGAGAAATGGGAAATGAGAA
13981   CATTCCAAGTACAGTGAGCACAATTAGCCGTAATAACATTAGAGAAAATGTTTTTAAAGA
14041   AGCCAGCTCAAGCAATATTAATGAAGTAGGTTCCAGTACTAATGAAGTGGGCTCCAGTAT
14101   TAATGAAATAGGTTCCAGTGATGAAAACATTCAAGCAGAACTAGGTAGAAACAGAGGGCC
14161   AAAATTGAATGCTATGCTTAGATTAGGGGTTTTGCAACCTGAGGTCTATAAACAAAGTCT
14221   TCCTGGAAGTAATTGTAAGCATCCTGAAATAAAAAAGCAAGAATATGAAGAAGTAGTTCA
14281   GACTGTTAATACAGATTTCTCTCCATATCTGATTTCAGATAACTTAGAACAGCCTATGGG
14341   AAGTAGTCATGCATCTCAGGTTTGTTCTGAGACACCTGATGACCTGTTAGATGATGGTGA
14401   AATAAAGGAAGATACTAGTTTTGCTGAAAATGACATTAAGGAAAGTTCTGCTGTTTTTAG
14461   CAAAAGCGTCCAGAAAGGAGAGCTTAGCAGGAGTCCTAGCCCTTTCACCCATACACATTT
14521   GGCTCAGGGTTACCGAAGAGGGGCCAAGAAATTAGAGTCCTCAGAAGAGAACTTATCTAG
14581   TGAGGATGAAGAGCTTCCCTGCTTCCAACACTTGTTATTTGGTAAAGTAAACAATATACC
14641   TTCTCAGTCTACTAGGCATAGCACCGTTGCTACCGAGTGTCTGTCTAAGAACACAGAGGA
14701   GAATTTATTATCATTGAAGAATAGCTTAAATGACTGCAGTAACCAGGTAATATTGGCAAA
14761   GGCATCTCAGGAACATCACCTTAGTGAGGAAACAAAATGTTCTGCTAGCTTGTTTTCTTC
14821   ACAGTGCAGTGAATTGGAAGACTTGACTGCAAATACAAACACCCAGGATCCTTTCTTGAT
14881   TGGTTCTTCCAAACAAATGAGGCATCAGTCTGAAAGCCAGGGAGTTGGTCTGAGTGACAA
14941   GGAATTGGTTTCAGATGATGAAGAAAGAGGAACGGGCTTGGAAGAAAATAATCAAGAAGA
15001   GCAAAGCATGGATTCAAACTTAGgtattggaaccaggtttttgtgtttgccccagtctat
15061   ttatagaagtgagctaaatgtttatgcttttggggagcacattttacaaatttccaagta
15121   tagttaaaggaactgcttcttaaacttgaaacatgttcctcctaaggtgcttttcataga
15181   aaaaagtccttcacacagctaggacgtcatctttgactgaatgagctttaacatcctaat
15241   tactggtggacttacttctggtttcattttataaagcaaatccggtgtcccaaagcaag
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FIG. 10E

```
15301  gaatttaatcatttgtgtgacatgaaagtaaatccagtcctgccaatgagaagaaaaag
15361  acacagcaagttgcagcgtttatagtctgcttttacatctgaacctctgtttttgttatt
15421  taagGTGAAGCAGCATCTGGGTGTGAGAGTGAAACAAGCGTCTCTGAAGACTGCTCAGGG
15481  CTATCCTCTCAGAGTGACATTTTAACCACTCaggtaaaaagcgtgtgtgtgtgtgcacat
15541  gcgtgtgtgtggtgtcctttgcattcagtagtatgtatcccacattcttaggtttgctga
15601  catcatctctttgaattaatggcacaattgtttgtggttcattgtcvvvvvvvvvvvvvn
15661  gngaatgtaatcctaatatttcncnccnacttaaaagaataccactccaanggcatcnca
15721  atacatcaatcaattggggaattgggattttccctcnctaacatcantggaataatttca
15781  tggcattaattgcatgaatgtggttagattaaaggtgttcatgctagaacttgtagttc
15841  catactaggtgatttcaattcctgtgctaaaattaatttgtatgatatattntcatttaa
15901  tggaaagcttctcaaagtatttcatttcttggtaccatttatcgtttttgaAGCAGAGG
15961  GATACCATGCAACATAACCTGATAAAGCTCCAGCAGGAAATGGCTGAACTAGAAGCTGTG
16021  TTAGAACAGCATGGGAGCCAGCCTTCTAACAGCTACCCTTCCATCATAAGTGACTCTTCT
16081  GCCCTTGAGGACCTGCGAAATCCAGAACAAAGCACATCAGAAAAAGgtgtgtattgttgg
16141  ccaaacactgatatcttaagcaaaattctttccttcccctttatctccttctgaagagta
16201  aggacctagctccaacattttatgatccttgctcagcacatgggtaattatggagccttg
16261  gttcttgtccctgctcacaactaatataccagtcagagggacccaaggcagtcattcatg
16321  ttgtcatctgagatacctacaacaagtagatgctatggggagcccatggvvvvvvvvvvv
16381  vvccattggtgctagcatctgtctgttgcattgcttgtttataaaattctgcctgata
16441  tacttgttaaaaaccaatttgtgtatcatagattgatgcttttgaaaaaaatcagtattc
16501  taacctgaattatcactatcagaacaaagcagtaaagtagatttgttttctcattccatt
16561  taaagCAGTATTAACTTCACAGAAAAGTAGTGAATACCCTATAAGCCAGAATCCAGAAGG
16621  CCTTTCTGCTGACAAGTTTGAGGTGTCTGCAGATAGTTCTACCAGTAAAAATAAAGAACC
16681  AGGAGTGGAAAGgtaagaaacatcaatgtaaagatgctgtggtatctgacatctttattt
16741  atattgaactctgattgttaatttttttcaccatactttctccagtttttttgcatacag
16801  gcatttatacacttttattgctctaggatacttcttttgtttaatcctatataggvvvvvv
16861  vvvvvvvvvggataagntcaagagatatttgataggtgatgcagtgatnaattgngaaaa
16921  tttnctgcctgcttttaatcttcccccgttcttccttcctncctcccctcccttcctncct
16981  cccgtccttncctttcctttccctccccttccnccttctttccntctntctttcctttctt
17041  tcctgtctacctttctttccttcctcccttcctttttcttttctttctttcctttcctttt
17101  ctttcctttctttcctttcctttctttcttgacagagtcttgctctgtcactcaggctgg
17161  agtgcagtggcgtgatctcgnctcactgcaacctctgtctcccaggttcaagcaattttc
17221  ctgcctcagcctcccgagtagctgagattacaggcgccagccaccacacccagctactga
17281  cctgcttttvvvvvvvvvvvvvaaacagctgggagatatggtgcctcagaccaaccccat
17341  gttatatgtcaaccctgacatattggcaggcaacatgaatccagacttctaggctgtcat
17401  gcgggctctttttgccagtcatttctgatctctctgacatgagctgtttcatttatgct
17461  ttggctgcccaggaagtatgatttgtcctttcacaattggtggcgatggttttctccttc
17521  catttatctttctagGTCATCCCCTTCTAAATGCCCATCATTAGATGATAGGTGGTACAT
17581  GCACAGTTGCTCTGGGAGTCTTCAGAATAGAAACTACCCATCTCAAGAGGAGCTCATTAA
17641  GGTTGTTGATGTGGAGGAGCAACAGCTGGAAGAGTCTGGGCCACACGATTTGACGGAAAC
17701  ATCTTACTTGCCAAGGCAAGATCTAGgtaatatttcatctgctgtattggaacaaacact
17761  ytgattttactctgaatcctacataaagatattctggttaaccaacttttagatgtacta
17821  gtctatcatggacacttttgttatacttaattaagcccactttagaaaaatagctcaagt
17881  gttaatcaaggtttacttgaaaattattgaaactgttaatccatctatattttaattaat
17941  ggtttaactaatgattttgaggatgwgggagtcktggtgtactctamatgtattatttca
18001  ggccaggcatagtggctcacgcctggtaatcccagtayycmrgagcccgaggcaggtgga
18061  gccagctgaggtcaggagttcaagacctgtcttggccaacatgggngaaaccctgtcttc
18121  ttcttaaaaaanacaaaaaaaattaactgggttgtgcttaggtgnatgccccgnatccta
18181  gttnttcttgngggttgagggaggagatcacnttggaccccggaggggngggtgggggng
18241  agcaggncaaaacacngacccagctggggtggaagggaagcccactcnaaaaaannttnv
18301  vvvvvvvvvvvvvttttaggaaacaagctactttggatttccaccaacacctgtattcat
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FIG. 10F

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18361  gtacccatttttctcttaacctaactttattggtctttttaattcttaacagagaccaga
18421  actttgtaattcaacattcatcgttgtgtaaattaaacttctcccattcctttcagAGGG
18481  AACCCCTTACCTGGAATCTGGAATCAGCCTCTTCTCTGATGACCCTGAATCTGATCCTTC
18541  TGAAGACAGAGCCCCAGAGTCAGCTCGTGTTGGCAACATACCATCTTCAACCTCTGCATT
18601  GAAAGTTCCCCAATTGAAAGTTGCAGAATCTGCCCAGAGTCCAGCTGCTGCTCATACTAC
18661  TGATACTGCTGGGTATAATGCAATGGAAGAAAGTGTGAGCAGGGAGAAGCCAGAATTGAC
18721  AGCTTCAACAGAAAGGGTCAACAAAAGAATGTCCATGGTGGTGTCTGGCCTGACCCCAGA
18781  AGAATTTgtgagtgtatccatatgtatctccctaatgactaagacttaacaacattctgg
18841  aaagagttttatgtaggtattgtcaattaataacctagaggaagaaatctagaaaacaat
18901  cacagttctgtgtaatttaatttcgattactaatttctgaaaatttagaayvvvvvvvvv
18961  vvvvncccnncccccnaatctgaaatgggggtaacccccccccaaccganacntgggtng
19021  cntagagantttaatggcccnttctgaggnacanaagcttaagccaggngacgtgggancn
19081  atgngttgtttnttgtttggttacctccagcctgggtgacagagcaagactctgtctaaa
19141  aaaaaaaaaaaaaaaaatcgactttaaatagttccaggacacgtgtagaacgtgcaggat
19201  tgctacgtaggtaaacatatgccatggtgggataactagtattctgagctgtgtgctaga
19261  ggtaactcatgataatggaatatttgatttaatttcagATGCTCGTGTACAAGTTTGCCA
19321  GAAAACACCACATCACTTTAACTAATCTAATTACTGAAGAGACTACTCATGTTGTTATGA
19381  AAACAGgtataccaagaacctttacagaataccttgcatctgctgcataaaaccacatga
19441  ggcgaggcacggtggcgcatgcctgtaatcgcagcactttgggaggccgaggcgggcaga
19501  tcacgagattaggagatcgagaccatcctggccagcatggtgaaaccccgtctctactan
19561  naaatggnaaaattanctgggtgtggtcgcgtgcncctgtagtcccagctactcgtgagg
19621  ctgaggcaggagaatcacttgaaccggggaaatggaggtttcagtgagcagagatcatnc
19681  ccctncattccagcctggcgacagagcaaggctccgtcnccnaaaaaataaaaaaaaacg
19741  tgaacaaataagaatatttgttgagcatagcatggatgatagtcttctaatagtcaatca
19801  attactttatgaaagacaaataatagttttgctgcttccttacctccttttgttttgggt
19861  taagatttggagtgtgggccaggcacvvvvvvvvvvvvvgatctatagctagccttggcg
19921  tctagaagatgggtgttgagaagagggagtggaaagatatttcctctggtcttaacttca
19981  tatcagcctcccctagacttccaaatatccatacctgctggttataattagtggtgtttt
20041  cagcctctgattctgtcaccaggggttttagaatcataaatccagattgatcttgggagt
20101  gtaaaaaactgaggctctttagcttcttaggacagcagttcctgattttgttttcaactt
20161  ctaatcctttgagtgtttttcattctgcagATGCTGAGTTTGTGTGTGAACGGACACTGA
20221  AATATTTTCTAGGAATTGCGGGAGGAAAATGGGTAGTTAGCTATTTCTgtaagtataata
20281  ctatttctcccctcctccctttaacacctcagaattgcatttttacacctaacatttaac
20341  acctaaggttttgctgatgctgagtctgagttaccaaaaggtctttaaattgtaatact
20401  aaactactttttatctttaatatcactttgttcaagataagctggtgatgctgggaaaatg
20461  ggtctcttttataactaataggacctaatctgctcctagcaatgttagcatatgagctag
20521  ggatttatttaatagtcggcaggaatccatgtgcarcagncaaacttataatgtttaaat
20581  taaacatcaactctgtctccagaaggaaactgctgctacaagccttattaaagggctgtg
20641  gctttagagggaaggacctctcctctgtcattcttcctgtgctcttttgtgaatcgctga
20701  cctctctatctccgtgaaaagagcacgttcttctgctgtatgtaacctgtcttttctatg
20761  atctctvvvvvvvvvvvvvnaaaaacggggnngggantgggccttaaanccaaagggcna
20821  actccccaaccattnaaaaantgacnggggattattaaaancggcgggaaacatttcacn
20881  gcccaactaatattgttaaattaaaaccaccaccnctgcnccaaggagggaaactgctgc
20941  tacaagccttattaaagggctgtggctttagagggaaggacctctcctctgtcattcttc
21001  ctgtgctcttttgtgaatcgctgacctctctatgtccgtgaaaagagcacgttcttcgtc
21061  tgtatgtaacctgtcttttctatgatctctttagGGGTGACCCAGTCTATTAAAGAAAGA
21121  AAAATGCTGAATGAGgtaagtacttgatgttacaaactaaccagagatattcattcagtc
21181  atatagttaaaaatgtatttgcttccttccatcaatgcaccactttccttaacaatgcac
21241  aaattttccatgataatgaggatcatcaagaattatgcaggcctgcactgtggctcatac
21301  ctataatcccagcgctttgggaggctgaggcgcttggatcvvvvvvvvvvvvvaattttt
21361  tgtatttttagtagagatgaggttcaccatgttggtctagatctggtgtcgaacgtcctg
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FIG. 10G

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21421  acctcaagtgatctgccagcctcagtctcccaaagtgctaggattacaggggtgagccac
21481  tgcgcctggcctgaatgcctaaaatatgacgtgtctgctccacttccattgaaggaagct
21541  tctctttctcttatcctgatgggttgtgtttggtttctttcagCATGATTTTGAAGTCAG
21601  AGGAGATGTGGTCAATGGAAGAAACCACCAAGGTCCAAAGCGAGCAAGAGAATCCCAGGA
21661  CAGAAAGgtaaagctccctccctcaagttgacaaaaatctcaccccaccactctgtattc
21721  cactcccctttgcagagatgggccgcttcattttgtaagacttattacatacatacacag
21781  tgctagatactttcacacaggttctttttcactcttccatcccaaccacataaataagt
21841  attgtctctactttatgaatgataaaactaagagatttagagaggctgtgtaatttggat
21901  tcccgtctcgggttcagatcvvvvvvvvvvvvvttggcctgattggtgacaaaagtgaga
21961  tgctcagtccttgaatgacaaagaatgcctgtagagttgcaggtccaactacatatgcac
22021  ttcaagaagatcttctgaaatctagtagtgttctggacattggactgcttgtccctggga
22081  agtagcagcagaaatgatcggtggtgaacagaagaaaaagaaaagctcttccttttgaa
22141  agtctgtttttgaataaaagccaatattcttttataactagattttccttctctccatt
22201  cccctgtccctctctcttcctctcttcttccagATCTTCAGGGGGCTAGAAATCTGTTGC
22261  TATGGGCCCTTCACCAACATGCCCACAGgtaagagcctgggagaaccccagagttccagc
22321  accagcctttgtcttacatagtggagtattataagcaaggtcccacgatgggggttcctc
22381  agattgctgaaatgttctagaggctattctatttctctaccactctccaaacaaaacagc
22441  acctaaatgttatcctatggcaaaaaaaaactataccttgtcccccttctcaagagcatg
22501  aaggtggttaatagttaggattcagtatgttatgtgttcagatggcgttgagctgctgtt
22561  agtgccvvvvvvvvvvvvvtttgagagactatcaaaccttataccaagtggccttatgga
22621  gactgataaccagagtacatggcatatcagtggcaaattgacttaaaatccataccccta
22681  ctattttaagaccattgtcctttggagcagagagacagactctcccattgagaggtcttg
22741  ctataagccttcatccggagagtgtagggtagagggcctgggttaagtatgcagattact
22801  gcagtgattttacatgtaaatgtccattttagATCAACTGGAATGGATGGTACAGCTGTG
22861  TGGTGCTTCTGTGGTGAAGGAGCTTTCATCATTCACCCTTGGCACAgtaagtattgggtg
22921  ccctgtcagtgtgggaggacacaatattctctcctgtgagcaagactggcacctgtcagt
22981  ccctatggatgcccctactgtagcctcagaagtcttctctgcccacatacctgtgccaaa
23041  agactccatvvvvvvvvvvvvvggtggtacgtgtctgtagttccagctacttgggaggct
23101  gagatggaaggattgcttgagcccaggaggcagaggtggnannttacgctgagatcacac
23161  cactgcactccagcctgggtgacagagcaagaccctgtctcaaaaacaaacaaaaaaaat
23221  gatgaagtgacagttccagtagtcctactttgacactttgaatgctctttccttcctggg
23281  gatccagGGTGTCCACCCAATTGTGGTTGTGCAGCCAGATGCCTGGACAGAGGACAATGG
23341  CTTCCATGgtaaggtgcctcgcatgtacctgtgctattagtggggtccttgtgcatgggt
23401  ttggtttatcactcattacctggtgcttgagtagcacagttcttggcacattttaaata
23461  tttgttgaatgaatggctaaaatgtctttttgatgtttttattgttatttgttttatatt
23521  gtaaaagtaatacatgaactgtttccatggggtgggagtaagatatgaatgttcatcacv
23581  vvvvvvvvvvvvcagtaatcctnagaactcatacgaccgggcccctggagtcgntgnttn
23641  gagcctagtccnggagaatgaattgacactaatctctgcttgtgttctctgtctccagCA
23701  ATTGGGCAGATGTGTGAGGCACCTGTGGTGACCCGAGAGTGGGTGTTGGACAGTGTAGCA
23761  CTCTACCAGTGCCAGGAGCTGGACACCTACCTGATACCCCAGATCCCCCACAGCCACTAC
23821  TGACTGCAGCCAGCCACAGGTACAGAGCCACAGGACCCCAAGAATGAGCTTACAAAGTGG
23881  CCTTTCCAGGCCCTGGGAGCTCCTCTCACTCTTCAGTCCTTCTACTGTCCTGGCTACTAA
23941  ATATTTTATGTACATCAGCCTGAAAAGGACTTCTGGCTATGCAAGGGTCCCTTAAAGATT
24001  TTCTGCTTGAAGTCTCCCTTGGAAAT
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FIG. 10H

LINKED BREAST AND OVARIAN CANCER SUSCEPTIBILITY GENE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of application Ser. No. 08/409,305 filed on 24 Mar. 1995, now abandoned, which is a continuation-in-part of application Ser. No. 08/348,824 filed on 29 Nov. 1994, now abandoned, which is a continuation-in-part of application Ser. No. 08/308,104 filed on 16 Sep. 1994, now abandoned, which is a continuation-in-part of application Ser. No. 08/300,266, filed on 2 Sep. 1994, now abandoned, which is a continuation-in-part of application Ser. No. 08/289,221, filed on 12 Aug. 1994, now abandoned, all incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates generally to the field of human genetics. Specifically, the present invention relates to methods and materials used to isolate and detect a human breast and ovarian cancer predisposing gene (BRCA1), some mutant alleles of which cause susceptibility to cancer, in particular, breast and ovarian cancer. More specifically, the invention relates to germline mutations in the BRCA1 gene and their use in the diagnosis of predisposition to breast and ovarian cancer. The present invention further relates to somatic mutations in the BRCA1 gene in human breast and ovarian cancer and their use in the diagnosis and prognosis of human breast and ovarian cancer. Additionally, the invention relates to somatic mutations in the BRCA1 gene in other human cancers and their use in the diagnosis and prognosis of human cancers. The invention also relates to the therapy of human cancers which have a mutation in the BRCA1 gene, including gene therapy, protein replacement therapy and protein mimetics. The invention further relates to the screening of drugs for cancer therapy. Finally, the invention relates to the screening of the BRCA1 gene for mutations, which are useful for diagnosing the predisposition to breast and ovarian cancer.

The publications and other materials used herein to illuminate the background of the invention, and in particular, cases to provide additional details respecting the practice, are incorporated herein by reference, and for convenience, are referenced by author and date in the following text and respectively grouped in the appended List of References.

BACKGROUND OF THE INVENTION

The genetics of cancer is complicated, involving multiple dominant, positive regulators of the transformed state (oncogenes) as well as multiple recessive, negative regulators (tumor suppressor genes). Over one hundred oncogenes have been characterized. Fewer than a dozen tumor suppressor genes have been identified, but the number is expected to increase beyond fifty (Knudson, 1993).

The involvement of so many genes underscores the complexity of the growth control mechanisms that operate in cells to maintain the integrity of normal tissue. This complexity is manifest in another way. So far, no single gene has been shown to participate in the development of all, or even the majority of human cancers. The most common oncogenic mutations are in the H-ras gene, found in 10–15% of all solid tumors (Anderson et al., 1992). The most frequently mutated tumor suppressor genes are the TP53 gene, homozygously deleted in roughly 50% of all minors, and CDKN2, which was homozygously deleted in 46% of tumor cell lines examined (Kamb et al., 1994). Without a target that is common to all transformed cells, the dream of a "magic bullet" that can destroy or revert cancer cells while leaving normal tissue unharmed is improbable. The hope for a new generation of specifically targeted antitumor drugs may rest on the ability to identify tumor suppressor genes or oncogenes that play general roles in control of cell division.

The minor suppressor genes which have been cloned and characterized influence susceptibility to: 1) Retinoblastoma (RB1); 2) Wilms' tumor (WT1); 3) Li-Fraumeni (TP53); 4) Familial adenomatous polyposis (APC); 5) Neurofibromatosis type 1 (NF1); 6) Neurofibromatosis type 2 (NF2); 7) von Hippel-Lindau syndrome (VHL); 8) Multiple endocrine neoplasia type 2A (MEN2A); and 9) Melanoma (CDKN2).

Tumor suppressor loci that have been mapped genetically but not yet isolated include genes for: Multiple endocrine neoplasia type 1 (MEN1); Lynch cancer family syndrome 2 (LCFS2); Neuroblastoma (NB); Basal cell nevus syndrome (BCNS); Beckwith-Wiedemann syndrome (BWS); Renal cell carcinoma (RCC); Tuberous sclerosis 1 (TSC1); and Tuberous sclerosis 2 (TSC2). The tumor suppressor genes that have been characterized to date encode products with similarities to a variety of protein types, including DNA binding proteins (WT1), ancillary transcription regulators (RB1), GTPase activating proteins or GAPs (NF1), cytoskeletal components (NF2), membrane bound receptor kinases (MEN2A), cell cycle regulators (CDKN2) and others with no obvious similarity to known proteins (APC and VHL).

In many cases, the tumor suppressor gene originally identified through genetic studies has been shown to be lost or mutated in some sporadic tumors. This result suggests that regions of chromosomal aberration may signify the position of important tumor suppressor genes involved both in genetic predisposition to cancer and in sporadic cancer.

One of the hallmarks of several tumor suppressor genes characterized to date is that they are deleted at high frequency in certain tumor types. The deletions often involve loss of a single allele, a so-called loss of heterozygosity (LOH), but may also involve homozygous deletion of both alleles. For LOH, the remaining allele is presumed to be nonfunctional, either because of a preexisting inherited mutation, or because of a secondary sporadic mutation.

Breast cancer is one of the most significant diseases that affects women. At the current rate, American women have a 1 in 8 risk of developing breast cancer by age 95 (American Cancer Society, 1992). Treatment of breast cancer at later stages is often futile and disfiguring, making early detection a high priority in medical management of the disease. Ovarian cancer, although less frequent than breast cancer is often rapidly fatal and is the fourth most common cause of cancer mortality in American women. Genetic factors contribute to an ill-defined proportion of breast cancer incidence, estimated to be about 5% of all cases but approximately 25% of cases diagnosed before age 40 (Claus et al., 1991). Breast cancer has been subdivided into two types, early-age onset and late-age onset, based on an inflection in the age-specific incidence curve around age 50. Mutation of one gene, BRCA1, is thought to account for approximately 45% of familial breast cancer, but at least 80% of families with both breast and ovarian cancer (Easton et al., 1993).

Intense efforts to isolate the BRCA1 gene have proceeded since it was first mapped in 1990 (Hall et al., 1990; Narod et al., 1991). A second locus, BRCA2, has recently been mapped to chromosome 13q (Wooster et al., 1994) and appears to account for a proportion of early-onset breast cancer roughly equal to BRCA1, but confers a lower risk of ovarian cancer. The remaining susceptibility to early-onset breast cancer is divided between as yet unmapped genes for familial cancer, and rarer germline mutations in genes such as TP53 (Malkin et al., 1990). It has also been suggested that heterozygote carriers for defective forms of the Ataxia-Telangectasia gene are at higher risk for breast cancer (Swift et al., 1976; Swift et al., 1991). Late-age onset breast cancer is also often familial although the risks in relatives are not as high as those for early-onset breast cancer (Cannon-Albright et al., 1994; Mettlin et al., 1990). However, the percentage of such cases due to genetic susceptibility is unknown.

Breast cancer has long been recognized to be, in part, a familial disease (Anderson, 1972). Numerous investigators have examined the evidence for genetic inheritance and concluded that the data are most consistent with dominant inheritance for a major susceptibility locus or loci (Bishop and Gardner, 1980; Go et al., 1983; Williams and Anderson, 1984; Bishop et al., 1988; Newman et al., 1988; Claus et al., 1991). Recent results demonstrate that at least three loci exist which convey susceptibility to breast cancer as well as other cancers. These loci are the TP53 locus on chromosome 17p (Malkin et al., 1990), a 17q-linked susceptibility locus known as BRCA1 (Hall et al., 1990), and one or more loci responsible for the unmapped residual. Hall et al. (1990) indicated that the inherited breast cancer susceptibility in kindreds with early age onset is linked to chromosome 17q21; although subsequent studies by this group using a more appropriate genetic model partially refuted the limitation to early onset breast cancer (Margaritte et al., 1992).

Most strategies for cloning the 17q-linked breast cancer predisposing gene (BRCA1) require precise genetic localization studies. The simplest model for the functional role of BRCA1 holds that alleles of BRCA1 that predispose to cancer are recessive to wild type alleles; that is, cells that contain at least one wild type BRCA1 allele are not cancerous. However, cells that contain one wild type BRCA1 allele and one predisposing allele may occasionally suffer loss of the wild type allele either by random mutation or by chromosome loss during cell division (nondisjunction). All the progeny of such a mutant cell lack the wild type function of BRCA1 and may develop into tumors. According to this model, predisposing alleles of BRCA1 are recessive, yet susceptibility to cancer is inherited in a dominant fashion: women who possess one predisposing allele (and one wild type allele) risk developing cancer, because their mammary epithelial cells may spontaneously lose the wild type BRCA1 allele. This model applies to a group of cancer susceptibility loci known as tumor suppressors or antioncogenes, a class of genes that includes the retinoblastoma gene and neurofibromatosis gene. By inference this model may also explain the BRCA1 function, as has recently been suggested (Smith et al., 1992).

A second possibility is that BRCA1 predisposing alleles are truly dominant; that is, a wild type allele of BRCA1 cannot overcome the tumor forming role of the predisposing allele. Thus, a cell that carries both wild type and mutant alleles would not necessarily lose the wild type copy of BRCA1 before giving rise to malignant cells. Instead, mammary cells in predisposed individuals would undergo some other stochastic change(s) leading to cancer.

If BRCA1 predisposing alleles are recessive, the BRCA1 gene is expected to be expressed in normal mammary tissue but not functionally expressed in mammary tumors. In contrast, if BRCA1 predisposing alleles are dominant, the wild type BRCA1 gene may or may not be expressed in normal mammary tissue. However, the predisposing allele will likely be expressed in breast tumor cells.

The 17q linkage of BRCA1 was independently confirmed in three of five kindreds with both breast cancer and ovarian cancer (Narod et al., 1991). These studies claimed to localize the gene within a very large region, 15 centiMorgans (cM), or approximately 15 million base pairs, to either side of the linked marker pCMM86 (D17S74). However, attempts to define the region further by genetic studies, using markers surrounding pCMM86, proved unsuccessful. Subsequent studies indicated that the gene was considerably more proximal (Easton et al., 1993) and that the original analysis was flawed (Margaritte et al., 1992). Hall et al., (1992) recently localized the BRCA1 gene to an approximately 8 cM interval (approximately 8 million base pairs) bounded by Mfd15 (D17S250) on the proximal side and the human GIP gene on the distal side. A slightly narrower interval for the BRCA1 locus, based on publicly available data, was agreed upon at the Chromosome 17 workshop in March of 1992 (Fain, 1992). The size of these regions and the uncertainty associated with them has made it exceedingly difficult to design and implement physical mapping and/or cloning strategies for isolating the BRCA1 gene.

Identification of a breast cancer susceptibility locus would permit the early detection of susceptible individuals and greatly increase our ability to understand the initial steps which lead to cancer. As susceptibility loci are often altered during tumor progression, cloning these genes could also be important in the development of better diagnostic and prognostic products, as well as better cancer therapies.

SUMMARY OF THE INVENTION

The present invention relates generally to the field of human genetics. Specifically, the present invention relates to methods and materials used to isolate and detect a human breast cancer predisposing gene (BRCA1), some alleles of which cause susceptibility to cancer, in particular breast and ovarian cancer. More specifically, the present invention relates to germline mutations in the BRCA1 gene and their use in the diagnosis of predisposition to breast and ovarian cancer. The invention further relates to somatic mutations in the BRCA1 gene in human breast cancer and their use in the diagnosis and prognosis of human breast and ovarian cancer. Additionally, the invention relates to somatic mutations in the BRCA1 gene in other human cancers and their use in the diagnosis and prognosis of human cancers. The invention also relates to the therapy of human cancers which have a mutation in the BRCA1 gene, including gene therapy, protein replacement therapy and protein mimetics. The invention further relates to the screening of drugs for cancer therapy. Finally, the invention relates to the screening of the BRCA1 gene for mutations, which are useful for diagnosing the predisposition to breast and ovarian cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a diagram showing the order of loci neighboring BRCA1 as determined by the chromosome 17 workshop. FIG. 1 is reproduced from Fain, 1992.

FIG. 2 is a schematic map of YACs which define part of Mfd15-Mfd188 region.

FIG. 3 is a schematic map of STSs, P1s and BACs in the BRCA1 region.

FIG. 4 is a schematic map of human chromosome 17. The pertinent region containing BRCA1 is expanded to indicate the relative positions of two previously identified genes, CA125 and RNU2. BRCA1 spans the marker D17S855.

FIG. 5 shows alignment of the BRCA1 zinc-finger domain with 3 other zinc-finger domains that scored highest in a Smith-Waterman alignment. RPT1 encodes a protein that appears to be a negative regulator of the IL-2 receptor in mouse. RIN1 encodes a DNA-binding protein that includes a RING-finger motif related to the zinc-finger. RFP1 encodes a putative transcription factor that is the N-terminal domain of the RET oncogene product. The bottom line contains the C3HC4 consensus zinc-finger sequence showing the positions of cysteines and one histidine that form the zinc ion binding pocket.

FIG. 6 is a diagram of BRCA1 mRNA showing the locations of introns and the variants of BRCA1 mRNA produced by alternative splicing. Intron locations are shown by dark triangles and the exons are numbered below the line representing the cDNA. The top cDNA is the composite used to generate the peptide sequence of BRCA1. Alternative forms identified as cDNA clones or hybrid selection clones are shown below.

FIG. 7 shows the tissue expression pattern of BRCA1. The blot was obtained from Clontech and contains RNA from the indicated tissues. Hybridization conditions were as recommended by the manufacturer using a probe consisting of nucleotide positions 3631 to 3930 of BRCA1. Note that both breast and ovary are heterogeneous tissues and the percentage of relevant epithelial cells can be variable. Molecular weight standards are in kilobases.

FIG. 8 is a diagram of the 5' untranslated region plus the beginning of the translated region of BRCA1 showing the locations of introns and the variants of BRCA1 mRNA produced by alternative splicing. Intron locations are shown by broken dashed lines. Six alternate splice forms are shown.

FIG. 9A shows a nonsense mutation in Kindred 2082. P indicates the person originally screened, b and c are haplotype carriers, a, d, e, f, and g do not carry the BRCA1 haplotype. The C to T mutation results in a stop codon and creates a site for the restriction enzyme AvrII. PCR amplification products are cut with this enzyme. The carriers are heterozygous for the site and therefore show three bands. Non-carriers remain uncut.

FIG. 9B shows a mutation and cosegregation analysis in BRCA1 kindreds. Carrier individuals are represented as filled circles and squares in the pedigree diagrams. Frameshift mutation in Kindred 1910. The first three lanes are control, noncarrier samples. Lanes labeled 1-3 contain sequences from carrier individuals. Lane 4 contains DNA from a kindred member who does not carry the BRCA1 mutation. The diamond is used to prevent identification of the kindred. The frameshift resulting from the additional C is apparent in lanes labeled 1, 2, and 3.

FIG. 9C shows a mutation and cosegregation analysis in BRCA1 kindreds. Carrier individuals are represented as filled circles and squares in the pedigree diagrams. Inferred regulatory mutation in Kindred 2035. ASO analysis of carriers and noncarriers of 2 different polymorphisms (PM1 and PM7) which were examined for heterozygosity in the germline and compared to the heterozygosity of lymphocyte mRNA. The top 2 rows of each panel contain PCR products amplified from genomic DNA and the bottom 2 rows contain PCR products amplified from cDNA. "A" and "G" are the two alleles detected by the ASO. The dark spots indicate that a particular allele is present in the sample. The first three lanes of PM7 represent the three genotypes in the general population.

FIGS. 10A–10H show genomic sequence of BRCA1 (SEQ ID NOS. 14–34). The lower case letters denote intron sequence while the upper case letters denote exon sequence. Indefinite intervals within introns are designated with vvvvvvvvvvvvv. Known polymorphic sites are shown as underlined and boldface type.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates generally to the field of human genetics. Specifically, the present invention relates to methods and materials used to isolate and detect a human breast cancer predisposing gene (BRCA1), some alleles of which cause susceptibility to cancer, in particular breast and ovarian cancer. More specifically, the present invention relates to germline mutations in the BRCA1 gene and their use in the diagnosis of predisposition to breast and ovarian cancer. The invention further relates to somatic mutations in the BRCA1 gene in human breast cancer and their use in the diagnosis and prognosis of human breast and ovarian cancer. Additionally, the invention relates to somatic mutations in the BRCA1 gene in other human cancers and their use in the diagnosis and prognosis of human cancers. The invention also relates to the therapy of human cancers which have a mutation in the BRCA1 gene, including gene therapy, protein replacement therapy and protein mimetics. The invention further relates to the screening of drugs for cancer therapy. Finally, the invention relates to the screening of the BRCA1 gene for mutations, which are useful for diagnosing the predisposition to breast and ovarian cancer.

The present invention provides an isolated polynucleotide comprising all, or a portion of the BRCA1 locus or of a mutated BRCA1 locus, preferably at least eight bases and not more than about 100 kb in length. Such polynucleotides may be antisense polynucleotides. The present invention also provides a recombinant construct comprising such an isolated polynucleotide, for example, a recombinant construct suitable for expression in a transformed host cell.

Also provided by the present invention are methods of detecting a polynucleotide comprising a portion of the BRCA1 locus or its expression product in an analyte. Such methods may further comprise the step of amplifying the portion of the BRCA1 locus, and may further include a step of providing a set of polynucleotides which are primers for amplification of said portion of the BRCA1 locus. The method is useful for either diagnosis of the predisposition to cancer or the diagnosis or prognosis of cancer.

The present invention also provides isolated antibodies, preferably monoclonal antibodies, which specifically bind to an isolated polypeptide comprised of at least five amino acid residues encoded by the BRCA1 locus.

The present invention also provides kits for detecting in an analyte a polynucleotide comprising a portion of the BRCA1 locus, the kits comprising a polynucleotide complementary to the portion of the BRCA1 locus packaged in a suitable container, and instructions for its use.

The present invention further provides methods of preparing a polynucleotide comprising polymerizing nucleotides to yield a sequence comprised of at least eight consecutive nucleotides of the BRCA1 locus; and methods of preparing a polypeptide comprising polymerizing amino acids to yield a sequence comprising at least five amino acids encoded within the BRCA1 locus.

The present invention further provides methods of screening the BRCA1 gene to identify mutations. Such methods may further comprise the step of amplifying a portion of the BRCA1 locus, and may further include a step of providing a set of polynucleotides which are primers for amplification of said portion of the BRCA1 locus. The method is useful for identifying mutations for use in either diagnosis of the predisposition to cancer or the diagnosis of cancer.

The present invention further provides methods of screening suspected BRCA1 mutant alleles to identify mutations in the BRCA1 gene.

In addition, the present invention provides methods of screening drugs for cancer therapy to identify suitable drugs for restoring BRCA1 gene product function.

Finally, the present invention provides the means necessary for production of gene-based therapies directed at cancer cells. These therapeutic agents may take the form of polynucleotides comprising all or a portion of the BRCA1 locus placed in appropriate vectors or delivered to target cells in more direct ways such that the function of the BRCA1 protein is reconstituted. Therapeutic agents may also take the form of polypeptides based on either a portion of, or the entire protein sequence of BRCA1. These may functionally replace the activity of BRCA1 in vivo.

It is a discovery of the present invention that the BRCA1 locus which predisposes individuals to breast cancer and ovarian cancer, is a gene encoding a BRCA1 protein, which has been found to have no significant homology with known protein or DNA sequences. This gene is termed BRCA1 herein. It is a discovery of the present invention that mutations in the BRCA1 locus in the germline are indicative of a predisposition to breast cancer and ovarian cancer. Finally, it is a discovery of the present invention that somatic mutations in the BRCA1 locus are also associated with breast cancer, ovarian cancer and other cancers, which represents an indicator of these cancers or of the prognosis of these cancers. The mutational events of the BRCA1 locus can involve deletions, insertions and point mutations within the coding sequence and the non-coding sequence.

Starting from a region on the long arm of human chromosome 17 of the human genome, 17q, which has a size estimated at about 8 million base pairs, a region which contains a genetic locus, BRCA1, which causes susceptibility to cancer, including breast and ovarian cancer, has been identified.

The region containing the BRCA1 locus was identified using a variety of genetic techniques. Genetic mapping techniques initially defined the BRCA1 region in terms of recombination with genetic markers. Based upon studies of large extended families ("kindreds") with multiple cases of breast cancer (and ovarian cancer cases in some kindreds), a chromosomal region has been pinpointed that contains the BRCA1 gene as well as other putative susceptibility alleles in the BRCA1 locus. Two meiotic breakpoints have been discovered on the distal side of the BRCA1 locus which are expressed as recombinants between genetic markers and the disease, and one recombinant on the proximal side of the BRCA1 locus. Thus, a region which contains the BRCA1 locus is physically bounded by these markers.

The use of the genetic markers provided by this invention allowed the identification of clones which cover the region from a human yeast artificial chromosome (YAC) or a human bacterial artificial chromosome (BAC) library. It also allowed for the identification and preparation of more easily manipulated cosmid, P1 and BAC clones from this region and the construction of a contig from a subset of the clones. These cosmids, P1s, YACs and BACs provide the basis for cloning the BRCA1 locus and provide the basis for developing reagents effective, for example, in the diagnosis and treatment of breast and/or ovarian cancer. The BRCA1 gene and other potential susceptibility genes have been isolated

from this region. The isolation was done using software trapping (a computational method for identifying sequences likely to contain coding exons, from contiguous or discontinuous genomic DNA sequences), hybrid selection techniques and direct screening, with whole or partial cDNA inserts from cosmids, P1s and BACs, in the region to screen cDNA libraries. These methods were used to obtain sequences of loci expressed in breast and other tissue. These candidate loci were analyzed to identify sequences which confer cancer susceptibility. We have discovered that there are mutations in the coding sequence of the BRCA1 locus in kindreds which are responsible for the 17q-linked cancer susceptibility known as BRCA1. This gene was not known to be in this region. The present invention not only facilitates the early detection of certain cancers, so vital to patient survival, but also permits the detection of susceptible individuals before they develop cancer.

Population Resources

Large, well-documented Utah kindreds are especially important in providing good resources for human genetic studies. Each large kindred independently provides the power to detect whether a BRCA1 susceptibility allele is segregating in that family. Recombinants informative for localization and isolation of the BRCA1 locus could be obtained only from kindreds large enough to confirm the presence of a susceptibility allele. Large sibships are especially important for studying breast cancer, since penetrance of the BRCA1 susceptibility allele is reduced both by age and sex, making informative sibships difficult to find. Furthermore, large sibships are essential for constructing haplotypes of deceased individuals by inference from the haplotypes of their close relatives.

While other populations may also provide beneficial information, such studies generally require much greater effort, and the families are usually much smaller and thus less informative. Utah's age-adjusted breast cancer incidence is 20% lower than the average U.S. rate. The lower incidence in Utah is probably due largely to an early age at first pregnancy, increasing the probability that cases found in Utah kindreds carry a genetic predisposition.

Genetic Mapping

Given a set of informative families, genetic markers are essential for linking a disease to a region of a chromosome. Such markers include restriction fragment length polymorphisms (RFLPs) (Botstein et al., 1980), markers with a viable number of tandem repeats (VNTRs) (Jeffreys et al., 1985; Nakamura et al., 1987), and an abundant class of DNA polymorphisms based on short tandem repeats (STRs), especially repeats of CpA (Weber and May, 1989; Litt et al., 1989). To generate a genetic map, one selects potential genetic markers and tests them using DNA extracted from members of the kindreds being studied.

Genetic markers useful in searching for a genetic locus associated with a disease can be selected on an ad hoc basis, by densely covering a specific chromosome, or by detailed analysis of a specific region of a chromosome. A preferred method for selecting genetic markers linked with a disease involves evaluating the degree of informativeness of kindreds to determine the ideal distance between genetic markers of a given degree of polymorphism, then selecting markers from known genetic maps which are ideally spaced for maximal efficiency. Informativeness of kindreds is measured by the probability that the markers will be heterozygous in unrelated individuals. It is also most efficient to use STR markers which are detected by amplification of the target nucleic acid sequence using PCR; such markers are highly informative, easy to assay (Weber and May, 1989), and can be assayed simultaneously using multiplexing strategies (Skolnick and Wallace, 1988), greatly reducing the number of experiments required.

Once linkage has been established, one needs to find markers that flank the disease locus, i.e., one or more markers proximal to the disease locus, and one or more markers distal to the disease locus. Where possible, candidate markers can be selected from a known genetic map. Where none is known, new markers can be identified by the STR technique, as shown in the Examples.

Genetic mapping is usually an iterative process. In the present invention, it began by defining flanking genetic markers around the BRCA1 locus, then replacing these flanking markers with other markers that were successively closer to the BRCA1 locus. As an initial step, recombination events, defined by large extended kindreds, helped specifically to localize the BRCA1 locus as either distal or proximal to a specific genetic marker (Goldgar et al., 1994).

The region surrounding BRCA1, until the disclosure of the present invention, was not well mapped and there were few markers. Therefore, short repetitive sequences on cosmids subcloned from YACs, which had been physically mapped, were analyzed in order to develop new genetic markers. Using this approach, one marker of the present invention, 42D6, was discovered which replaced pCMM86 as the distal flanking marker for the BRCA1 region. Since 42D6 is approximately 14 cM from pCMM86, the BRCA1 region was thus reduced by approximately 14 centiMorgans (Easton et al., 1993). The present invention thus began by finding a much more closely linked distal flanking marker of the BRCA1 region. BRCA1 was then discovered to be distal to the genetic marker Mfd15. Therefore, BRCA1 was shown to be in a region of 6 to 10 million bases bounded by Mfd15 and 42D6. Marker Mfd191 was subsequently discovered to be distal to Mfd15 and proximal to BRCA1. Thus, Mfd15 was replaced with Mfd191 as the closest proximal genetic marker. Similarly, it was discovered that genetic marker Mfd188 could replace genetic marker 42D6, narrowing the region containing the BRCA1 locus to approximately 1.5 million bases. Then the marker Mfd191 was replaced with tdj1474 as the proximal marker and Mfd188 was replaced with U5R as the distal marker, further narrowing the BRCA1 region to a small enough region to allow isolation and characterization of the BRCA1 locus (see FIG. 3), using techniques known in the art and described herein.

Physical Mapping

Three distinct methods were employed to physically map the region. The first was the use of yeast artificial chromosomes (YACs) to clone the region which is flanked by tdj1474 and U5R. The second was the creation of a set of P1, BAC and cosmid clones which cover the region containing the BRCA1 locus.

Yeast Artificial Chromosomes (YACs). Once a sufficiently small region containing the BRCA1 locus was identified, physical isolation of the DNA in the region proceeded by identifying a set of overlapping YACs which covers the region. Useful YACs can be isolated from known libraries, such as the St. Louis and CEPH YAC libraries, which are widely distributed and contain approximately 50,000 YACs each. The YACs isolated were from these publicly accessible libraries and can be obtained from a number of sources including the Michigan Genome Center. Clearly, others who had access to these YACs, without the disclosure of the present invention, would not have known the value of the specific YACs we selected since they would not have known which YACs were within, and which YACs outside of, the smallest region containing the BRCA1 locus.

Cosmid, P1 and BAC Clones. In the present invention, it is advantageous to proceed by obtaining cosmid, P1, and BAC clones to cover this region. The smaller size of these inserts, compared to YAC inserts, makes them more useful as specific hybridization probes. Furthermore, having the cloned DNA in bacterial cells, rather than in yeast cells, greatly increases the ease with which the DNA of interest can be manipulated, and improves the signal-to-noise ratio of hybridization assays. For cosmid subclones of YACs, the DNA is partially digested with the restriction enzyme Sau3A and cloned into the BamHI site of the pWE15 cosmid vector (Stratagene, cat. #1251201). The cosmids containing human sequences are screened by hybridization with human repetitive DNA (e.g., Gibco/BRL, Human C_0t-1 DNA, cat. 5279SA), and then fingerprinted by a variety of techniques, as detailed in the Examples.

P1 and BAC clones are obtained by screening libraries constructed from the total human genome with specific sequence tagged sites (STSs) derived from the YACs, cosmids or P1s and BACs, isolated as described herein.

These P1, BAC and cosmid clones can be compared by interspersed repetitive sequence (IRS) PCR and/or restriction enzyme digests followed by gel electrophoresis and comparison of the resulting DNA fragments ("fingerprints") (Maniatis et al., 1982). The clones can also be characterized by the presence of STSs. The fingerprints are used to define an overlapping contiguous set of clones which covers the region but is not excessively redundant, referred to herein as a "minimum tiling path". Such a minimum tiling path forms the basis for subsequent experiments to identify cDNAs which may originate from the BRCA1 locus.

Coverage of the Gap with P1 and BAC Clones. To cover any gaps in the BRCA1 contig between the identified cosmids with genomic clones, clones in P1 and BAC vectors which contain inserts of genomic DNA roughly twice as large as cosmids for P1s and still greater for BACs (Sternberg, 1990; Sternberg et al., 1990; Pierce et al., 1992; Shizuya et al., 1992) were used. P1 clones were isolated by Genome Sciences using PCR primers provided by us for screening. BACs were provided by hybridization techniques in Dr. Mel Simon's laboratory. The strategy of using P1 clones also permitted the covering of the genomic region with an independent set of clones not derived from YACs. This guards against the possibility of other deletions in YACs that have not been detected. These new sequences derived from the P1 clones provide the material for further screening for candidate genes, as described below.

Gene Isolation

There are many techniques for testing genomic clones for the presence of sequences likely to be candidates for the coding sequence of a locus one is attempting to isolate, including but not limited to:

a. zoo blots

b. identifying HTF islands

c. exon trapping

d. hybridizing cDNA to cosmids or YACs.

e. screening cDNA libraries.

(a) Zoo blots. The first technique is to hybridize cosmids to Southern blots to identify DNA sequences which are evolutionarily conserved, and which therefore give positive hybridization signals with DNA from species of varying degrees of relationship to humans (such as monkey, cow, chicken, pig, mouse and rat). Southern blots containing such DNA from a variety of species are commercially available (Clonetech, Cat. 7753-1).

(b) Identifing HTF islands. The second technique involves finding regions rich in the nucleotides C and G, which often occur near or within coding sequences. Such sequences are called HTF (HpaI tiny fragment) or CpG islands, as restriction enzymes specific for sites which contain CpG dimers cut frequently in these regions (Lindsay et al., 1987).

(c) Exon trapping. The third technique is exon trapping, a method that identifies sequences in genomic DNA which contain splice junctions and therefore are likely to comprise coding sequences of genes. Exon amplification (Buckler et al., 1991) is used to select and amplify exons from DNA clones described above. Exon amplification is based on the selection of RNA sequences which are flanked by functional 5' and/or 3' splice sites. The products of the exon amplification are used to screen the breast cDNA libraries to identify a manageable number of candidate genes for further study. Exon trapping can also be performed on small segments of sequenced DNA using computer programs or by software trapping.

(d) Hybridizing cDNA to Cosmids, P1s, BACs or YACs. The fourth technique is a modification of the selective enrichment technique which utilizes hybridization of cDNA to cosmids, P1 s, BACs or YACs and permits transcribed sequences to be identified in, and recovered from cloned genomic DNA (Kandpal et al., 1990). The selective enrichment technique, as modified for the present purpose, involves binding DNA from the region of BRCA1 present in a YAC to a column matrix and selecting cDNAs from the relevant libraries which hybridize with the bound DNA, followed by amplification and purification of the bound DNA, resulting in a great enrichment for cDNAs in the region represented by the cloned genomic DNA.

(e) Identification of cDNAs. The fifth technique is to identify cDNAs that correspond to the BRCA1 locus. Hybridization probes containing putative coding sequences, selected using any of the above techniques, are used to screen various libraries, including breast tissue cDNA libraries, ovarian cDNA libraries, and any other necessary libraries.

Another variation on the theme of direct selection of cDNA was also used to find candidate genes for BRCA1 (Lovett et al., 1991; Futreal, 1993). This method uses cosmid, P1 or BAC DNA as the probe. The probe DNA is digested with a blunt cutting restriction enzyme such as HaeIII. Double stranded adapters are then ligated onto the DNA and serve as binding sites for primers in subsequent PCR amplification reactions using biotinylated primers. Target cDNA is generated from mRNA derived from tissue samples, e.g., breast tissue, by synthesis of either random primed or oligo(dT) primed first strand followed by second strand synthesis. The cDNA ends are rendered blunt and ligated onto double-stranded adapters. These adapters serve as amplification sites for PCR. The target and probe sequences are denatured and mixed with human C_0t-1 DNA to block repetitive sequences. Solution hybridization is carried out to high C_0t-1/2 values to ensure hybridization of rare target cDNA molecules. The annealed material is then captured on avidin beads, washed at high stringency and the retained cDNAs are eluted and amplified by PCR. The selected cDNA is subjected to further rounds of enrichment before cloning into a plasmid vector for analysis.

Testing the cDNA for Candidacy

Proof that the cDNA is the BRCA1 locus is obtained by finding sequences in DNA extracted from affected kindred members which create abnormal BRCA1 gene products or abnormal levels of BRCA1 gene product. Such BRCA1 susceptibility alleles will co-segregate with the disease in large kindreds. They will also be present at a much higher frequency in non-kindred individuals with breast and ovarian cancer then in individuals in the general population. Finally, since tumors often mutate somatically at loci which are in other instances mutated in the germline, we expect to see normal germline BRCA1 alleles mutated into sequences which are identical or similar to BRCA1 susceptibility alleles in DNA extracted from tumor tissue. Whether one is comparing BRCA1 sequences from tumor tissue to BRCA1 alleles from the germline of the same individuals, or one is comparing germline BRCA1 alleles from cancer cases to those from unaffected individuals, the key is to find mutations which are serious enough to cause obvious disruption to the normal function of the gene product. These mutations can take a number of forms. The most severe forms would be frame shift mutations or large deletions which would cause the gene to code for an abnormal protein or one which would significantly alter protein expression. Less severe disruptive mutations would include small in-frame deletions and nonconservative base pair substitutions which would have a significant effect on the protein produced, such as changes to or from a cysteine residue, from a basic to an acidic amino acid or vice versa, from a hydrophobic to hydrophilic amino acid or vice versa, or other mutations which would affect secondary, tertiary or quaternary protein structure. Silent mutations or those resulting in conservative amino acid substitutions would not generally be expected to disrupt protein function.

According to the diagnostic and prognostic method of the present invention, alteration of the wild-type BRCA1 locus is detected. In addition, the method can be performed by detecting the wild-type BRCA1 locus and confirming the lack of a predisposition to cancer at the BRCA1 locus. "Alteration of a wild-type gene" encompasses all forms of mutations including deletions, insertions and point mutations in the coding and noncoding regions. Deletions may be of the entire gene or of only a portion of the gene. Point mutations may result in stop codons, frameshift mutations or amino acid substitutions. Somatic mutations are those which occur only in certain tissues, e.g., in the tumor tissue, and are not inherited in the germline. Germline mutations can be found in any of a body's tissues and are inherited. If only a single allele is somatically mutated, an early neoplastic state is indicated. However, if both alleles are somatically mutated, then a late neoplastic state is indicated. The finding of BRCA1 mutations thus provides both diagnostic and prognostic information. A BRCA1 allele which is not deleted (e.g., found on the sister chromosome to a chromosome carrying a BRCA1 deletion) can be screened for other mutations, such as insertions, small deletions, and point mutations. It is believed that many mutations found in tumor tissues will be those leading to decreased expression of the BRCA1 gene product. However, mutations leading to nonfunctional gene products would also lead to a cancerous state. Point mutational events may occur in regulatory regions, such as in the promoter of the gene, leading to loss or diminution of expression of the mRNA. Point mutations may also abolish proper RNA processing, leading to loss of expression of the BRCA1 gene product, or to a decrease in mRNA stability or translation efficiency.

Useful diagnostic techniques include, but are not limited to fluorescent in situ hybridization (FISH), direct DNA sequencing, PFGE analysis, Southern blot analysis, single stranded conformation analysis (SSCA), RNase protection assay, allele-specific oligonucleotide (ASO), dot blot analysis and PCR-SSCP, as discussed in detail further below.

Predisposition to cancers, such as breast and ovarian cancer, and the other cancers identified herein, can be ascertained by testing any tissue of a human for mutations of the BRCA1 gene. For example, a person who has inherited a germline BRCA1 mutation would be prone to develop cancers. This can be determined by testing DNA from any tissue of the person's body. Most simply, blood can be drawn and DNA extracted from the cells of the blood. In addition, prenatal diagnosis can be accomplished by testing fetal cells, placental cells or amniotic cells for mutations of the BRCA1 gene. Alteration of a wild-type BRCA1 allele, whether, for example, by point mutation or deletion, can be detected by any of the means discussed herein.

There are several methods that can be used to detect DNA sequence variation. Direct DNA sequencing, either manual sequencing or automated fluorescent sequencing can detect sequence variation. For a gene as large as BRCA1, manual sequencing is very labor-intensive, but under optimal conditions, mutations in the coding sequence of a gene are rarely missed. Another approach is the single-stranded conformation polymorphism assay (SSCA) (Orita et al., 1989). This method does not detect all sequence changes, especially if the DNA fragment size is greater than 200 bp, but can be optimized to detect most DNA sequence variation. The reduced detection sensitivity is a disadvantage, but the increased throughput possible with SSCA makes it an attractive, viable alternative to direct sequencing for mutation detection on a research basis. The fragments which have shifted mobility on SSCA gels are then sequenced to determine the exact nature of the DNA sequence variation. Other approaches based on the detection of mismatches between the two complementary DNA strands include clamped denaturing gel electrophoresis (CDGE) (Sheffield et al., 1991), heteroduplex analysis (HA) (White et al., 1992) and chemical mismatch cleavage (CMC) (Grompe et al., 1989). None of the methods described above will detect large deletions, duplications or insertions, nor will they detect a regulatory mutation which affects transcription or translation of the protein. Other methods which might detect these classes of mutations such as a protein truncation assay or the asymmetric assay, detect only specific types of mutations and would not detect missense mutations. A review of currently available methods of detecting DNA sequence variation can be found in a recent review by Grompe (1993). Once a mutation is known, an allele specific detection approach such as allele specific oligonucleotide (ASO) hybridization can be utilized to rapidly screen large numbers of other samples for that same mutation.

In order to detect the alteration of the wild-type BRCA1 gene in a tissue, it is helpful to isolate the tissue free from surrounding normal tissues. Means for enriching tissue preparation for tumor cells are known in the art. For example, the tissue may be isolated from paraffin or cryostat sections. Cancer cells may also be separated from normal cells by flow cytometry. These techniques, as well as other techniques for separating tumor cells from normal cells, are well known in the art. If the tumor tissue is highly contaminated with normal cells, detection of mutations is more difficult.

A rapid preliminary analysis to detect polymorphisms in DNA sequences can be performed by looking at a series of Southern blots of DNA cut with one or more restriction enzymes, preferably with a large number of restriction enzymes. Each blot contains a series of normal individuals and a series of cancer cases, tumors, or both. Southern blots displaying hybridizing fragments (differing in length from control DNA when probed with sequences near or including the BRCA1 locus) indicate a possible mutation. If restriction enzymes which produce very large restriction fragments are used, then pulsed field gel electrophoresis (PFGE) is employed.

Detection of point mutations may be accomplished by molecular cloning of the BRCA1 allele(s) and sequencing the allele(s) using techniques well known in the art. Alternatively, the gene sequences can be amplified directly from a genomic DNA preparation from the minor tissue, using known techniques. The DNA sequence of the amplified sequences can then be determined.

There are six well known methods for a more complete, yet still indirect, test for confirming the presence of a susceptibility allele: 1) single stranded conformation analysis (SSCA) (Orita et al., 1989); 2) denaturing gradient gel electrophoresis (DGGE) (Wartell et al., 1990; Sheffield et al., 1989); 3) RNase protection assays (Finkelstein et al., 1990; Kinszler et al., 1991); 4) allele-specific oligonucleotides (ASOs) (Conner et al., 1983); 5) the use of proteins which recognize nucleotide mismatches, such as the *E. coli* mutS protein (Modrich, 1991); and 6) allele-specific PCR (Rano & Kidd, 1989). For allele-specific PCR, primers are used which hybridize at their 3' ends to a particular BRCA1 mutation. If the particular BRCA1 mutation is not present, an amplification product is not observed. Amplification Refractory Mutation System (ARMS) can also be used, as disclosed in European Patent Application Publication No. 0332435 and in Newton et al., 1989. Insertions and deletions of genes can also be detected by cloning, sequencing and amplification. In addition, restriction fragment length polymorphism (RFLP) probes for the gene or surrounding marker genes can be used to score alteration of an allele or an insertion in a polymorphic fragment. Such a method is particularly useful for screening relatives of an affected individual for the presence of the BRCA1 mutation found in that individual. Other techniques for detecting insertions and deletions as known in the art can be used.

In the first three methods (SSCA, DGGE and RNase protection assay), a new electrophoretic band appears. SSCA detects a band which migrates differentially because the sequence change causes a difference in single-strand, intramolecular base pairing. RNase protection involves cleavage of the mutant polynucleotide into two or more smaller fragments. DGGE detects differences in migration rates of mutant sequences compared to wild-type sequences, using a denaturing gradient gel. In an allele-specific oligonucleotide assay, an oligonucleotide is designed which detects a specific sequence, and the assay is performed by detecting the presence or absence of a hybridization signal. In the mutS assay, the protein binds only to sequences that contain a nucleotide mismatch in a heteroduplex between mutant and wild-type sequences.

Mismatches, according to the present invention, are hybridized nucleic acid duplexes in which the two strands are not 100% complementary. Lack of total homology may be due to deletions, insertions, inversions or substitutions. Mismatch detection can be used to detect point mutations in the gene or in its mRNA product. While these techniques are less sensitive than sequencing, they are simpler to perform on a large number of tumor samples. An example of a mismatch cleavage technique is the RNase protection method. In the practice of the present invention, the method involves the use of a labeled riboprobe which is complementary to the human wild-type BRCA1 gene coding sequence. The riboprobe and either mRNA or DNA isolated from the tumor tissue are annealed (hybridized) together and subsequently digested with the enzyme RNase A which is able to detect some mismatches in a duplex RNA structure. If a mismatch is detected by RNase A, it cleaves at the site of the mismatch. Thus, when the annealed RNA preparation is separated on an electrophoretic gel matrix, if a mismatch has been detected and cleaved by RNase A, an RNA product will be seen which is smaller than the full length duplex RNA for the riboprobe and the mRNA or DNA. The riboprobe need not be the full length of the BRCA1 mRNA or gene but can be a segment of either. If the riboprobe comprises only a segment of the BRCA1 mRNA or gene, it will be desirable to use a number of these probes to screen the whole mRNA sequence for mismatches.

In similar fashion, DNA probes can be used to detect mismatches, through enzymatic or chemical cleavage. See, e.g., Cotton et al., 1988; Shenk et al., 1975; Novack et al., 1986. Alternatively, mismatches can be detected by shifts in the electrophoretic mobility of mismatched duplexes relative to matched duplexes. See, e.g., Cariello, 1988. With either riboprobes or DNA probes, the cellular mRNA or DNA which might contain a mutation can be amplified using PCR (see below) before hybridization. Changes in DNA of the BRCA1 gene can also be detected using Southern hybridization, especially if the changes are gross rearrangements, such as deletions and insertions.

DNA sequences of the BRCA1 gene which have been amplified by use of PCR may also be screened using allele-specific probes. These probes are nucleic acid oligomers, each of which contains a region of the BRCA1 gene sequence harboring a known mutation. For example, one oligomer may be about 30 nucleotides in length, corresponding to a portion of the BRCA1 gene sequence. By use of a battery of such allele-specific probes, PCR amplification products can be screened to identify the presence of a previously identified mutation in the BRCA1 gene. Hybridization of allele-specific probes with amplified BRCA1 sequences can be performed, for example, on a nylon filter. Hybridization to a particular probe under stringent hybridization conditions indicates the presence of the same mutation in the tumor tissue as in the allele-specific probe.

The most definitive test for mutations in a candidate locus is to directly compare genomic BRCA1 sequences from cancer patients with those from a control population. Alternatively, one could sequence messenger RNA after amplification, e.g., by PCR, thereby eliminating the necessity of determining the exon structure of the candidate gene.

Mutations from cancer patients falling outside the coding region of BRCA1 can be detected by examining the noncoding regions, such as introns and regulatory sequences near or within the BRCA1 gene. An early indication that mutations in noncoding regions are important may come from Northern blot experiments that reveal messenger RNA molecules of abnormal size or abundance in cancer patients as compared to control individuals.

Alteration of BRCA1 mRNA expression can be detected by any techniques known in the art. These include Northern blot analysis, PCR amplification and RNase protection. Diminished mRNA expression indicates an alteration of the wild-type BRCA1 gene. Alteration of wild-type BRCA1 genes can also be detected by screening for alteration of wild-type BRCA1 protein. For example, monoclonal antibodies immunoreactive with BRCA1 can be used to screen a tissue. Lack of cognate antigen would indicate a BRCA1 mutation. Antibodies specific for products of mutant alleles could also be used to detect mutant BRCA1 gene product. Such immunological assays can be done in any convenient formats known in the art. These include Western blots, immunohistochemical assays and ELISA assays. Any means for detecting an altered BRCA1 protein can be used to detect alteration of wild-type BRCA1 genes. Functional assays, such as protein binding determinations, can be used. In addition, assays can be used which detect BRCA1 biochemical function. Finding a mutant BRCA1 gene product indicates alteration of a wild-type BRCA1 gene.

Mutant BRCA1 genes or gene products can also be detected in other human body samples, such as serum, stool, urine and sputum. The same techniques discussed above for detection of mutant BRCA1 genes or gene products in tissues can be applied to other body samples. Cancer cells are sloughed off from tumors and appear in such body samples. In addition, the BRCA1 gene product itself may be secreted into the extracellular space and found in these body samples even in the absence of cancer cells. By screening such body samples, a simple early diagnosis can be achieved for many types of cancers. In addition, the progress of chemotherapy or radiotherapy can be monitored more easily by testing such body samples for mutant BRCA1 genes or gene products.

The methods of diagnosis of the present invention are applicable to any tumor in which BRCA1 has a role in tumorigenesis. The diagnostic method of the present invention is useful for clinicians, so they can decide upon an appropriate course of treatment.

The primer pairs of the present invention are useful for determination of the nucleotide sequence of a particular BRCA1 allele using PCR. The pairs of single-stranded DNA primers can be annealed to sequences within or surrounding the BRCA1 gene on chromosome 17q21 in order to prime amplifying DNA synthesis of the BRCA1 gene itself. A complete set of these primers allows synthesis of all of the nucleotides of the BRCA1 gene coding sequences, i.e., the exons. The set of primers preferably allows synthesis of both intron and exon sequences. Allele-specific primers can also be used. Such primers anneal only to particular-BRCA1 mutant alleles, and thus will only amplify a product in the presence of the mutant allele as a template.

In order to facilitate subsequent cloning of amplified sequences, primers may have restriction enzyme site sequences appended to their 5' ends. Thus, all nucleotides of the primers are derived from BRCA1 sequences or sequences adjacent to BRCA1, except for the few nucleotides necessary to form a restriction enzyme site. Such enzymes and sites are well known in the art. The primers themselves can be synthesized using techniques which are well known in the art. Generally, the primers can be made using oligonucleotide synthesizing machines which are commercially available. Given the sequence of the BRCA1 open reading frame shown in SEQ ID NO:1, design of particular primers is well within the skill of the art.

The nucleic acid probes provided by the present invention are useful for a number of purposes. They can be used in Southern hybridization to genomic DNA and in the RNase protection method for detecting point mutations already discussed above. The probes can be used to detect PCR amplification products. They may also be used to detect mismatches with the BRCA1 gene or mRNA using other techniques.

It has been discovered that individuals with the wild-type BRCA1 gene do not have cancer which results from the BRCA1 allele. However, mutations which interfere with the function of the BRCA1 protein are involved in the pathogenesis of cancer. Thus, the presence of an altered (or a mutant) BRCA1 gene which produces a protein having a loss of function, or altered function, directly correlates to an increased risk of cancer. In order to detect a BRCA1 gene mutation, a biological sample is prepared and analyzed for a difference between the sequence of the BRCA1 allele being analyzed and the sequence of the wild-type BRCA1 allele. Mutant BRCA1 alleles can be initially identified by any of the techniques described above. The mutant alleles are then sequenced to identify the specific mutation of the particular mutant allele. Alternatively, mutant BRCA1 alleles can be initially identified by identifying mutant (altered) BRCA1 proteins, using conventional techniques. The mutant alleles are then sequenced to identify the specific mutation for each allele. The mutations, especially those which lead to an altered function of the BRCA1 protein, are then used for the diagnostic and prognostic methods of the present invention.

Definitions

The present invention employs the following definitions:

"Amplification of Polynucleotides" utilizes methods such as the polymerase chain reaction (PCR), ligation amplification (or ligase chain reaction, LCR) and amplification methods based on the use of Q-beta replicase. These methods are well known and widely practiced in the art. See, e.g., U.S. Pat. Nos. 4,683,195 and 4,683,202 and Innis et al., 1990 (for PCR); and Wu et al., 1989a (for LCR). Reagents and hardware for conducting PCR are commercially available. Primers useful to amplify sequences from the BRCA1 region are preferably complementary to, and hybridize specifically to sequences in the BRCA1 region or in regions that flank a target region therein. BRCA1 sequences generated by amplification may be sequenced directly. Alternatively, but less desirably, the amplified sequence(s) may be cloned prior to sequence analysis. A method for the direct cloning and sequence analysis of enzymatically amplified genomic segments has been described by Scharf, 1986.

"Analyte polynucleotide" and "analyte strand" refer to a single- or double-stranded polynucleotide which is suspected of containing a target sequence, and which may be present in a variety of types of samples, including biological samples.

"Antibodies." The present invention also provides polyclonal and/or monoclonal antibodies and fragments thereof, and immunologic binding equivalents thereof, which are capable of specifically binding to the BRCA1 polypeptides and fragments thereof or to polynucleotide sequences from the BRCA1 region, particularly from the BRCA1 locus or a portion thereof. The term "antibody" is used both to refer to a homogeneous molecular entity, or a mixture such as a serum product made up of a plurality of different molecular entities. Polypeptides may be prepared synthetically in a peptide synthesizer and coupled to a carrier molecule (e.g., keyhole limpet hemocyanin) and injected over several months into rabbits. Rabbit sera is tested for immunoreactivity to the BRCA1 polypeptide or fragment. Monoclonal antibodies may be made by injecting mice with the protein polypeptides, fusion proteins or fragments thereof. Monoclonal antibodies will be screened by ELISA and tested for specific immunoreactivity with BRCA1 polypeptide or fragments thereof. See, Harlow & Lane, 1988. These antibodies will be useful in assays as well as pharmaceuticals.

Once a sufficient quantity of desired polypeptide has been obtained, it may be used for various purposes. A typical use is the production of antibodies specific for binding. These antibodies may be either polyclonal or monoclonal, and may be produced by in vitro or in vivo techniques well known in the art. For production of polyclonal antibodies, an appropriate target immune system, typically mouse or rabbit, is selected. Substantially purified antigen is presented to the immune system in a fashion determined by methods appropriate for the animal and by other parameters well known to immunologists. Typical sites for injection are in footpads, intramuscularly, intraperitoneally, or intradermally. Of course, other species may be substituted for mouse or rabbit. Polyclonal antibodies are then purified using techniques known in the art, adjusted for the desired specificity.

An immunological response is usually assayed with an immunoassay. Normally, such immunoassays involve some purification of a source of antigen, for example, that produced by the same cells and in the same fashion as the antigen. A variety of immunoassay methods are well known in the art. See, e.g., Harlow & Lane, 1988, or Goding, 1986.

Monoclonal antibodies with affinities of 10^{-8} M^{-1} or preferably 10^{-9} to 10^{-10} M^{-1} or stronger will typically be made by standard procedures as described, e.g., in Harlow & Lane, 1988 or Goding, 1986. Briefly, appropriate animals will be selected and the desired immunization protocol followed. After the appropriate period of time, the spleens of such animals are excised and individual spleen cells fused, typically, to immortalized myeloma cells under appropriate selection conditions. Thereafter, the cells are clonally separated and the supernatants of each clone tested for their production of an appropriate antibody specific for the desired region of the antigen.

Other suitable techniques involve in vitro exposure of lymphocytes to the antigenic polypeptides, or alternatively, to selection of libraries of antibodies in phage or similar vectors. See Huse et al., 1989. The polypeptides and antibodies of the present invention may be used with or without modification. Frequently, polypeptides and antibodies will be labeled by joining, either covalently or non-covalently, a substance which provides for a detectable signal. A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent agents, chemiluminescent agents, magnetic particles and the like. Patents teaching the use of such labels include U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149 and 4,366,241. Also, recombinant immunoglobulins may be produced (see U.S. Pat. No. 4,816,567).

"Binding partner" refers to a molecule capable of binding a ligand molecule with high specificity, as for example, an antigen and an antigen-specific antibody or an enzyme and its inhibitor. In general, the specific binding partners must bind with sufficient affinity to immobilize the analyte copy/complementary strand duplex (in the case of polynucleotide hybridization) under the isolation conditions. Specific binding partners are known in the art and include, for example, biotin and avidin or streptavidin, IgG and protein A, the numerous, known receptor-ligand couples, and complementary polynucleotide strands. In the case of complementary polynucleotide binding partners, the partners are normally at least about 15 bases in length, and may be at least 40 bases in length. The polynucleotides may be composed of DNA, RNA, or synthetic nucleotide analogs.

A "biological sample" refers to a sample of tissue or fluid suspected of containing an analyte polynucleotide or polypeptide from an individual including, but not limited to, e.g., plasma, serum, spinal fluid, lymph fluid, the external sections of the skin, respiratory, intestinal, and genitourinary tracts, tears, saliva, blood cells, tumors, organs, tissue and samples of in vitro cell culture constituents.

As used herein, the terms "diagnosing" or "prognosing," as used in the context of neoplasia, are used to indicate 1) the classification of lesions as neoplasia, 2) the determination of the severity of the neoplasia, or 3) the monitoring of the disease progression, prior to, during and after treatment.

"Encode". A polynucleotide is said to "encode" a polypeptide if, in its native state or when manipulated by methods well known to those skilled in the art, it can be transcribed and/or translated to produce the mRNA for and/or the polypeptide or a fragment thereof. The anti-sense strand is the complement of such a nucleic acid, and the encoding sequence can be deduced therefrom.

"Isolated" or "substantially pure". An "isolated" or "substantially pure" nucleic acid (e.g., an RNA, DNA or a mixed polymer) is one which is substantially separated from other cellular components which naturally accompany a native human sequence or protein, e.g., ribosomes, polymerases, many other human genome sequences and proteins. The term embraces a nucleic acid sequence or protein which has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems.

"BRCA1 Allele" refers to normal alleles of the BRCA1 locus as well as alleles carrying variations that predispose individuals to develop cancer of many sites including, for example, breast, ovarian, colorectal and prostate cancer. Such predisposing alleles are also called "BRCA1 susceptibility alleles".

"BRCA1 Locus," "BRCA1 Gene," "BRCA1 Nucleic Acids" or "BRCA1 Polynucleotide" each refer to polynucleotides, all of which are in the BRCA1 region, that are likely to be expressed in normal tissue, certain alleles of which predispose an individual to develop breast, ovarian, colorectal and prostate cancers. Mutations at the BRCA1 locus may be involved in the initiation and/or progression of other types of tumors. The locus is indicated in part by mutations that predispose individuals to develop cancer. These mutations fall within the BRCA1 region described infra. The BRCA1 locus is intended to include coding sequences, intervening sequences and regulatory elements controlling transcription and/or translation. The BRCA1 locus is intended to include all allelic variations of the DNA sequence.

These terms, when applied to a nucleic acid, refer to a nucleic acid which encodes a BRCA1 polypeptide, fragment, homolog or variant, including, e.g., protein fusions or deletions. The nucleic acids of the present invention will possess a sequence which is either derived from, or substantially similar to a natural BRCA1-encoding gene or one having substantial homology with a natural BRCA1-encoding gene or a portion thereof. The coding sequence for a BRCA1 polypeptide is shown in SEQ ID NO: 1, with the amino acid sequence shown in SEQ ID NO:2.

The polynucleotide compositions of this invention include RNA, cDNA, genomic DNA, synthetic forms, and mixed polymers, both sense and antisense strands, and may be chemically or biochemically modified or may contain non-natural or derivatized nucleotide bases, as will be readily appreciated by those skilled in the art. Such modifications include, for example, labels, methylation, substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoamidates, carbamates, etc.), charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), pendent moieties (e.g., polypeptides), intercalators (e.g., acridine, psoralen, etc.), chelators, alkylators, and modified linkages (e.g., alpha anomeric nucleic acids, etc.). Also included are synthetic molecules that mimic polynucleotides in their ability to bind to a designated sequence via hydrogen bonding and other chemical interactions. Such molecules are known in the art and include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule.

The present invention provides recombinant nucleic acids comprising all or part of the BRCA1 region. The recombinant construct may be capable of replicating autonomously in a host cell. Alternatively, the recombinant construct may become integrated into the chromosomal DNA of the host cell. Such a recombinant polynucleotide comprises a polynucleotide of genomic, cDNA, semi-synthetic, or synthetic origin which, by virtue of its origin or manipulation, 1) is not associated with all or a portion of a polynucleotide with which it is associated in nature; 2) is linked to a polynucleotide other than that to which it is linked in nature; or 3) does not occur in nature.

Therefore, recombinant nucleic acids comprising sequences otherwise not naturally occurring are provided by this invention. Although the wild-type sequence may be employed, it will often be altered, e.g., by deletion, substitution or insertion.

cDNA or genomic libraries of various types may be screened as natural sources of the nucleic acids of the present invention, or such nucleic acids may be provided by amplification of sequences resident in genomic DNA or other natural sources, e.g., by PCR. The choice of cDNA libraries normally corresponds to a tissue source which is abundant in mRNA for the desired proteins. Phage libraries are normally preferred, but other types of libraries may be used. Clones of a library are spread onto plates, transferred to a substrate for screening, denatured and probed for the presence of desired sequences.

The DNA sequences used in this invention will usually comprise at least about five codons (15 nucleotides), more usually at least about 7–15 codons, and most preferably, at least about 35 codons. One or more introns may also be present. This number of nucleotides is usually about the minimal length required for a successful probe that would hybridize specifically with a BRCA1-encoding sequence.

Techniques for nucleic acid manipulation are described generally, for example, in Sambrook et al., 1989 or Ausubel et al., 1992. Reagents useful in applying such techniques, such as restriction enzymes and the like, are widely known in the art and commercially available from such vendors as New England BioLabs, Boehringer Mannheim, Amersham, Promega Biotec, U.S. Biochemicals, New England Nuclear, and a number of other sources. The recombinant nucleic acid sequences used to produce fusion proteins of the present invention may be derived from natural or synthetic sequences. Many natural gene sequences are obtainable from various cDNA or from genomic libraries using appropriate probes. See, GenBank, National Institutes of Health.

"BRCA1 Region" refers to a portion of human chromosome 17q21 bounded by the markers tdj1474 and U5R. This region contains the BRCA1 locus, including the BRCA1 gene.

As used herein, the terms "BRCA1 locus," "BRCA1 allele" and "BRCA1 region" all refer to the double-stranded DNA comprising the locus, allele, or region, as well as either of the single-stranded DNAs comprising the locus, allele or region.

As used herein, a "portion" of the BRCA1 locus or region or allele is defined as having a minimal size of at least about eight nucleotides, or preferably about 15 nucleotides, or more preferably at least about 25 nucleotides, and may have a minimal size of at least about 40 nucleotides.

"BRCA1 protein" or "BRCA1 polypeptide" refer to a protein or polypeptide encoded by the BRCA1 locus, variants or fragments thereof. The term "polypeptide" refers to a polymer of amino acids and its equivalent and does not refer to a specific length of the product; thus, peptides, oligopeptides and proteins are included within the definition of a polypeptide. This term also does not refer to, or exclude modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations, and the like. Included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, natural amino acids, etc.), polypeptides with substituted linkages as well as other modifications known in the art, both naturally and non-naturally occurring. Ordinarily, such polypeptides will be at least about 50% homologous to the native BRCA1 sequence, preferably in excess of about 90%, and more preferably at least about 95% homologous. Also included are proteins encoded by DNA which hybridize under high or low stringency conditions, to BRCA1-encoding nucleic acids and closely related polypeptides or proteins retrieved by antisera to the BRCA1 protein (s).

The length of polypeptide sequences compared for homology will generally be at least about 16 amino acids, usually at least about 20 residues, more usually at least about 24 residues, typically at least about 28 residues, and preferably more than about 35 residues.

"Operably linked" refers to a juxtaposition wherein the components so described are in a relationship permitting them to function in their intended manner. For instance, a promoter is operably linked to a coding sequence if the promoter affects its transcription or expression.

"Probes". Polynucleotide polymorphisms associated with BRCA1 alleles which predispose to certain cancers or are associated with most cancers are detected by hybridization with a polynucleotide probe which forms a stable hybrid with that of the target sequence, under stringent to moderately stringent hybridization and wash conditions. If it is expected that the probes will be perfectly complementary to the target sequence, stringent conditions will be used. Hybridization stringency may be lessened if some mismatching is expected, for example, if variants are expected with the result that the probe will not be completely complementary. Conditions are chosen which rule out nonspecific/adventitious bindings, that is, which minimize noise. Since such indications identify neutral DNA polymorphisms as well as mutations, these indications need further analysis to demonstrate detection of a BRCA1 susceptibility allele.

Probes for BRCA1 alleles may be derived from the sequences of the BRCA1 region or its cDNAs. The probes may be of any suitable length, which span all or a portion of the BRCA1 region, and which allow specific hybridization to the BRCA1 region. If the target sequence contains a sequence identical to that of the probe, the probes may be short, e.g., in the range of about 8–30 base pairs, since the hybrid will be relatively stable under even stringent conditions. If some degree of mismatch is expected with the probe, i.e., if it is suspected that the probe will hybridize to a variant region, a longer probe may be employed which hybridizes to the target sequence with the requisite specificity.

The probes will include an isolated polynucleotide attached to a label or reporter molecule and may be used to isolate other polynucleotide sequences, having sequence similarity by standard methods. For techniques for preparing and labeling probes see, e.g., Sambrook et al., 1989 or Ausubel et al., 1992. Other similar polynucleotides may be selected by using homologous polynucleotides. Alternatively, polynucleotides encoding these or similar polypeptides may be synthesized or selected by use of the redundancy in the genetic code. Various codon substitutions may be introduced, e.g., by silent changes (thereby producing various restriction sites) or to optimize expression for a particular system. Mutations may be introduced to modify the properties of the polypeptide, perhaps to change ligand-binding affinities, interchain affinities, or the polypeptide degradation or turnover rate.

Probes comprising synthetic oligonucleotides or other polynucleotides of the present invention may be derived from naturally occurring or recombinant single- or double-stranded polynucleotides, or be chemically synthesized. Probes may also be labeled by nick translation, Klenow fill-in reaction, or other methods known in the art.

Portions of the polynucleotide sequence having at least about eight nucleotides, usually at least about 15 nucleotides, and fewer than about 6 kb, usually fewer than about 1.0 kb, from a polynucleotide sequence encoding BRCA1 are preferred as probes. The probes may also be used to determine whether mRNA encoding BRCA1 is present in a cell or tissue.

"Protein modifications or fragments" are provided by the present invention for BRCA1 poly-peptides or fragments thereof which are substantially homologous to primary structural sequence but which include, e.g., in vivo or in vitro chemical and biochemical modifications or which incorporate unusual amino acids. Such modifications include, for example, acetylation, carboxylation, phosphorylation, glycosylation, ubiquitination, labeling, e.g., with radionuclides, and various enzymatic modifications, as will be readily appreciated by those well skilled in the art. A variety of methods for labeling polypeptides and of substituents or labels useful for such purposes are well known in the art, and include radioactive isotopes such as ^{32}p, ligands which bind to labeled antiligands (e.g., antibodies), fluorophores, chemiluminescent agents, enzymes, and antiligands which can serve as specific binding pair members for a labeled ligand. The choice of label depends on the sensitivity required, ease of conjugation with the primer, stability requirements, and available instrumentation. Methods of labeling polypeptides are well known in the art. See, e.g., Sambrook et al., 1989 or Ausubel et al., 1992.

Besides substantially full-length polypeptides, the present invention provides for biologically active fragments of the polypeptides. Significant biological activities include ligand-binding, immunological activity and other biological activities characteristic of BRCA1 polypeptides. Immunological activities include both immunogenic function in a target immune system, as well as sharing of immunological epitopes for binding, serving as either a competitor or substitute antigen for an epitope of the BRCA1 protein. As used herein, "epitope" refers to an antigenic determinant of a polypeptide. An epitope could comprise three amino acids in a spatial conformation which is unique to the epitope. Generally, an epitope consists of at least five such amino acids, and more usually consists of at least 8–10 such amino acids. Methods of determining the spatial conformation of such amino acids are known in the art.

For immunological purposes, tandem-repeat polypeptide segments may be used as immunogens, thereby producing highly antigenic proteins. Alternatively, such polypeptides will serve as highly efficient competitors for specific binding. Production of antibodies specific for BRCA1 polypeptides or fragments thereof is described below.

The present invention also provides for fusion polypeptides, comprising BRCA1 polypeptides and fragments. Homologous polypeptides may be fusions between two or more BRCA1 polypeptide sequences or between the sequences of BRCA1 and a related protein. Likewise, heterologous fusions may be constructed which would exhibit a combination of properties or activities of the derivative proteins. For example, ligand-binding or other domains may be "swapped" between different new fusion polypeptides or fragments. Such homologous or heterologous fusion polypeptides may display, for example, altered strength or specificity of binding. Fusion partners include immunoglobulins, bacterial β-galactosidase, trpE, protein A, β-lactamase, alpha amylase, alcohol dehydrogenase and yeast alpha mating factor. See, e.g., Godowski et al., 1988.

Fusion proteins will typically be made by either recombinant nucleic acid methods, as described below, or may be chemically synthesized. Techniques for the synthesis of polypeptides are described, for example, in Merrifield, 1963.

"Protein purification" refers to various methods for the isolation of the BRCA1 polypeptides from other biological material, such as from cells transformed with recombinant nucleic acids encoding BRCA1, and are well known in the art. For example, such polypeptides may be purified by immuno-affinity chromatography employing, e.g., the antibodies provided by the present invention. Various methods of protein purification are well known in the art, and include those described in Deutscher, 1990 and Scopes, 1982.

The terms "isolated", "substantially pure", and "substantially homogeneous" are used interchangeably to describe a protein or polypeptide which has been separated from components which accompany it in its natural state. A monomeric protein is substantially pure when at least about 60 to 75% of a sample exhibits a single polypeptide sequence. A substantially pure protein will typically comprise about 60 to 90% W/W of a protein sample, more usually about 95%, and preferably will be over about 99% pure. Protein purity or homogeneity may be indicated by a number of means well known in the art, such as polyacrylamide gel electrophoresis of a protein sample, followed by visualizing a single polypeptide band upon staining the gel. For certain purposes, higher resolution may be provided by using HPLC or other means well known in the art which are utilized for application.

A BRCA1 protein is substantially free of naturally associated components when it is separated from the native contaminants which accompany it in its natural state. Thus, a polypeptide which is chemically synthesized or synthesized in a cellular system different from the cell from which it naturally originates will be substantially free from its naturally associated components. A protein may also be rendered substantially free of naturally associated components by isolation, using protein purification techniques well known in the art.

A polypeptide produced as an expression product of an isolated and manipulated genetic sequence is an "isolated polypeptide," as used herein, even if expressed in a homologous cell type. Synthetically made forms or molecules expressed by heterologous cells are inherently isolated molecules.

"Recombinant nucleic acid" is a nucleic acid which is not naturally occurring, or which is made by the artificial combination of two otherwise separated segments of sequence. This artificial combination is often accomplished by either chemical syntheses means, or by the artificial manipulation of isolated segments of nucleic acids, by genetic engineering techniques. Such is usually done to replace a codon with a redundant codon encoding the same or a conservative amino acid, while typically introducing or removing a sequence recognition site. Alternatively, it is performed to join together nucleic acid segments of desired functions to generate a desired combination of functions.

"Regulatory sequences" refers to those sequences normally within 100 kb of the coding region of a locus, but they may also be more distant from the coding region, which affect the expression of the gene (including transcription of the gene, and translation, splicing, stability or the like of the messenger RNA).

"Substantial homologous or similarity". A nucleic acid or fragment thereof is "substantially homologous" ("or substantially similar") to another if, when optimally aligned (with appropriate nucleotide insertions or deletions) with the other nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 60% of the nucleotide bases, usually at least about 70%, more usually at least about 80%, preferably at least about 90%, and more preferably at least about 95–98% of the nucleotide bases.

Alternatively, substantial homology or (similarity) exists when a nucleic acid or fragment thereof will hybridize to another nucleic acid (or a complementary strand thereof) under selective hybridization conditions, to a strand, or to its complement. Selectivity of hybridization exists when hybridization which is substantially more selective than total lack of specificity occurs. Typically, selective hybridization will occur when there is at least about 55% homology over a stretch of at least about 14 nucleotides, preferably at least about 65%, more preferably at least about 75%, and most preferably at least about 90%. See, Kanehisa, 1984. The length of homology comparison, as described, may be over longer stretches, and in certain embodiments will often be over a stretch of at least about nine nucleotides, usually at least about 20 nucleotides, more usually at least about 24 nucleotides, typically at least about 28 nucleotides, more typically at least about 32 nucleotides, and preferably at least about 36 or more nucleotides.

Nucleic acid hybridization will be affected by such conditions as salt concentration, temperature, or organic solvents, in addition to the base composition, length of the complementary strands, and the number of nucleotide base mismatches between the hybridizing nucleic acids, as will be readily appreciated by those skilled in the art. Stringent temperature conditions will generally include temperatures in excess of 30° C., typically in excess of 37° C., and preferably in excess of 45° C. Stringent salt conditions will ordinarily be less than 1000 mM, typically less than 500 mM, and preferably less than 200 mM. However, the combination of parameters is much more important than the measure of any single parameter. See, e.g., Wetmur & Davidson, 1968.

Probe sequences may also hybridize specifically to duplex DNA under certain conditions to form triplex or other higher order DNA complexes. The preparation of such probes and suitable hybridization conditions are well known in the art.

The terms "substantial homology" or "substantial identity", when referring to polypeptides, indicate that the polypeptide or protein in question exhibits at least about 30% identity with an entire naturally-occurring protein or a portion thereof, usually at least about 70% identity, and preferably at least about 95% identity.

"Substantially similar function" refers to the function of a modified nucleic acid or a modified protein, with reference to the wild-type BRCA1 nucleic acid or wild-type BRCA1 polypeptide. The modified polypeptide will be substantially homologous to the wild-type BRCA1 polypeptide and will have substantially the same function. The modified polypeptide may have an altered amino acid sequence and/or may contain modified amino acids. In addition to the similarity of function, the modified polypeptide may have other useful properties, such as a longer half-life. The similarity of function (activity) of the modified polypeptide may be substantially the same as the activity of the wild-type BRCA1 polypeptide. Alternatively, the similarity of function (activity) of the modified polypeptide may be higher than the activity of the wild-type BRCA1 polypeptide. The modified polypeptide is synthesized using conventional techniques, or is encoded by a modified nucleic acid and produced using conventional techniques. The modified nucleic acid is prepared by conventional techniques. A nucleic acid with a function substantially similar to the wild-type BRCA1 gene function produces the modified protein described above.

Homology, for polypeptides, is typically measured using sequence analysis software. See, e.g., the Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 910 University Avenue, Madison, Wisconsin 53705. Protein analysis software matches similar sequences using measure of homologous assigned to various substitutions, deletions and other modifications. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine.

A polypeptide "fragment," "portion" or "segment" is a stretch of amino acid residues of at least about five to seven contiguous amino acids, often at least about seven to nine contiguous amino acids, typically at least about nine to 13 contiguous amino acids and, most preferably, at least about 20 to 30 or more contiguous amino acids.

The polypeptides of the present invention, if soluble, may be coupled to a solid-phase support, e.g., nitrocellulose, nylon, column packing materials (e.g., Sepharose beads), magnetic beads, glass wool, plastic, metal, polymer gels, cells, or other substrates. Such supports may take the form, for example, of beads, wells, dipsticks, or membranes.

"Target region" refers to a region of the nucleic acid which is amplified and/or detected. The term "target sequence" refers to a sequence with which a probe or primer will form a stable hybrid under desired conditions.

The practice of the present invention employs, unless otherwise indicated, conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA, genetics, and immunology. See, e.g., Maniatis et al., 1982; Sambrook et al., 1989; Ausubel et al., 1992; Glover, 1985; Anand, 1992; Guthrie & Fink, 1991. A general discussion of techniques and materials for human gene mapping, including mapping of human chromosome 17q, is provided, e.g., in White and Lalouel, 1988.

Preparation of recombinant or chemically synthesized nucleic acids; vectors, transformation, host cells

Large amounts of the polynucleotides of the present invention may be produced by replication in a suitable host cell. Natural or synthetic polynucleotide fragments coding for a desired fragment will be incorporated into recombinant polynucleotide constructs, usually DNA constructs, capable of introduction into and replication in a prokaryotic or eukaryotic cell. Usually the polynucleotide constructs will be suitable for replication in a unicellular host, such as yeast or bacteria, but may also be intended for introduction to (with and without integration within the genome) cultured mammalian or plant or other eukaryotic cell lines. The purification of nucleic acids produced by the methods of the present invention is described, e.g., in Sambrook et al., 1989 or Ausubel et al., 1992.

The polynucleotides of the present invention may also be produced by chemical synthesis, e.g., by the phosphoramidite method described by Beaucage & Carruthers, 1981 or the triester method according to Matteucci and Caruthers, 1981, and may be performed on commercial, automated oligonucleotide synthesizers. A double-stranded fragment may be obtained from the single-stranded product of chemical synthesis either by synthesizing the complementary strand and annealing the strands together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Polynucleotide constructs prepared for introduction into a prokaryotic or eukaryotic host may comprise a replication system recognized by the host, including the intended polynucleotide fragment encoding the desired polypeptide, and will preferably also include transcription and translational initiation regulatory sequences operably linked to the polypeptide encoding segment. Expression vectors may include, for example, an origin of replication or autonomously replicating sequence (ARS) and expression control sequences, a promoter, an enhancer and necessary processing information sites, such as ribosome-binding sites, RNA splice sites, polyadenylation sites, transcriptional terminator sequences, and mRNA stabilizing sequences. Secretion signals may also be included where appropriate, whether from a native BRCA1 protein or from other receptors or from secreted polypeptides of the same or related species, which allow the protein to cross and/or lodge in cell membranes, and thus attain its functional topology, or be secreted from the cell. Such vectors may be prepared by means of standard recombinant techniques well known in the art and discussed, for example, in Sambrook et al., 1989 or Ausubel et al. 1992.

An appropriate promoter and other necessary vector sequences will be selected so as to be functional in the host, and may include, when appropriate, those naturally associated with BRCA1 genes. Examples of workable combinations of cell lines and expression vectors are described in Sambrook et al., 1989 or Ausubel et al., 1992; see also, e.g., Metzger et al., 1988. Many useful vectors are known in the art and may be obtained from such vendors as Stratagene, New England Biolabs, Promega Biotech, and others. Promoters such as the trp, lac and phage promoters, tRNA promoters and glycolytic enzyme promoters may be used in prokaryotic hosts. Useful yeast promoters include promoter regions for metallothionein, 3-phosphoglycerate kinase or other glycolytic enzymes such as enolase or glyceraldehyde-3-phosphate dehydrogenase, enzymes responsible for maltose and galactose utilization, and others. Vectors and promoters suitable for use in yeast expression are further described in Hitzeman et al., EP 73,675A. Appropriate non-native mammalian promoters might include the early and late promoters from SV40 (Fiers et al., 1978) or promoters derived from murine Moloney leukemia virus, mouse tumor virus, avian sarcoma viruses, adenovirus II, bovine papilloma virus or polyoma. In addition, the construct may be joined to an amplifiable gene (e.g., DHFR) so that multiple copies of the gene may be made. For appropriate enhancer and other expression control sequences, see also *Enhancers and Eukaryotic Gene Expression*, Cold Spring Harbor Press, Cold Spring Harbor, New York (1983).

While such expression vectors may replicate autonomously, they may also replicate by being inserted into the genome of the host cell, by methods well known in the art.

Expression and cloning vectors will likely contain a selectable marker, a gene encoding a protein necessary for survival or growth of a host cell transformed with the vector. The presence of this gene ensures growth of only those host cells which express the inserts. Typical selection genes encode proteins that a) confer resistance to antibiotics or other toxic substances, e.g. ampicillin, neomycin, methotrexate, etc.; b) complement auxotrophic deficiencies, or c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for Bacilli. The choice of the proper selectable marker will depend on the host cell, and appropriate markers for different hosts are well known in the art.

The vectors containing the nucleic acids of interest can be transcribed in vitro, and the resulting RNA introduced into the host cell by well-known methods, e.g., by injection (see, Kubo et al., 1988), or the vectors can be introduced directly into host cells by methods well known in the art, which vary depending on the type of cellular host, including electroporation; transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; infection (where the vector is an infectious agent, such as a retroviral genome); and other methods. See generally, Sambrook et al., 1989 and Ausubel *et al.*, 1992. The introduction of the polynucleotides into the host cell by any method known in the art, including, inter alia, those described above, will be referred to herein as "transformation." The cells into which have been introduced nucleic acids described above are meant to also include the progeny of such cells.

Large quantities of the nucleic acids and polypeptides of the present invention may be prepared by expressing the BRCA1 nucleic acids or portions thereof in vectors or other expression vehicles in compatible prokaryotic or eukaryotic host cells. The most commonly used prokaryotic hosts are strains of *Escherichia coli*, although other prokaryotes, such as *Bacillus subtilis* or Pseudomonas may also be used.

Mammalian or other eukaryotic host cells, such as those of yeast, filamentous fungi, plant, insect, or amphibian or avian species, may also be useful for production of the proteins of the present invention. Propagation of mammalian cells in culture is per se well known. See, Jakoby and Pastan, 1979. Examples of commonly used mammalian host cell lines are VERO and HeLa cells, Chinese hamster ovary (CHO) cells, and WI38, BHK, and COS cell lines, although it will be appreciated by the skilled practitioner that other cell lines may be appropriate, e.g., to provide higher expression, desirable glycosylation patterns, or other features.

Clones are selected by using markers depending on the mode of the vector construction. The marker may be on the same or a different DNA molecule, preferably the same DNA molecule. In prokaryotic hosts, the transformant may be selected, e.g., by resistance to ampicillin, tetracycline or other antibiotics. Production of a particular product based on temperature sensitivity may also serve as an appropriate marker.

Prokaryotic or eukaryotic cells transformed with the polynucleotides of the present invention will be useful not only for the production of the nucleic acids and polypeptides of the present invention, but also, for example, in studying the characteristics of BRCA1 polypeptides.

Antisense polynucleotide sequences are useful in preventing or diminishing the expression of the BRCA1 locus, as will be appreciated by those skilled in the art. For example, polynucleotide vectors containing all or a portion of the BRCA1 locus or other sequences from the BRCA1 region (particularly those flanking the BRCA1 locus) may be placed under the control of a promoter in an antisense orientation and introduced into a cell. Expression of such an antisense construct within a cell will interfere with BRCA1 transcription and/or translation and/or replication.

The probes and primers based on the BRCA1 gene sequences disclosed herein are used to identify homologous BRCA1 gene sequences and proteins in other species. These BRCA1 gene sequences and proteins are used in the diagnostic/prognostic, therapeutic and drug screening methods described herein for the species from which they have been isolated.

Method of Use: Nucleic Acid Diagnosis and Diagnostic Kits

In order to detect the presence of a BRCA1 allele predisposing an individual to cancer, a biological sample such as blood is prepared and analyzed for the presence or absence of susceptibility alleles of BRCA1. In order to detect the presence of neoplasia, the progression toward malignancy of a precursor lesion, or as a prognostic indicator, a biological sample of the lesion is prepared and analyzed for the presence or absence of mutant alleles of BRCA1. Results of these tests and interpretive information are returned to the health care provider for communication to the tested individual. Such diagnoses may be performed by diagnostic laboratories, or, alternatively, diagnostic kits are manufactured and sold to health care providers or to private individuals for self-diagnosis.

Initially, the screening method involves amplification of the relevant BRCA1 sequences. In another preferred embodiment of the invention, the screening method involves a non-PCR based strategy. Such screening methods include two-step label amplification methodologies that are well known in the art. Both PCR and non-PCR based screening strategies can detect target sequences with a high level of sensitivity.

The most popular method used today is target amplification. Here, the target nucleic acid sequence is amplified with polymerases. One particularly preferred method using polymerase-driven amplification is the polymerase chain reaction (PCR). The polymerase chain reaction and other polymerase-driven amplification assays can achieve over a million-fold increase in copy number through the use of polymerase-driven amplification cycles. Once amplified, the resulting nucleic acid can be sequenced or used as a substrate for DNA probes.

When the probes are used to detect the presence of the target sequences (for example, in screening for cancer susceptibility), the biological sample to be analyzed, such as blood or serum, may be treated, if desired, to extract the nucleic acids. The sample nucleic acid may be prepared in various ways to facilitate detection of the target sequence; e.g. denaturation, restriction digestion, electrophoresis or dot blotting. The targeted region of the analyte nucleic acid usually must be at least partially single-stranded to form hybrids with the targeting sequence of the probe. If the sequence is naturally single-stranded, denaturation will not be required. However, if the sequence is double-stranded, the sequence will probably need to be denatured. Denaturation can be carried out by various techniques known in the art.

Analyte nucleic acid and probe are incubated under conditions which promote stable hybrid formation of the target sequence in the probe with the putative targeted sequence in the analyte. The region of the probes which is used to bind to the analyte can be made completely complementary to the targeted region of human chromosome 17q. Therefore, high stringency conditions are desirable in order to prevent false positives. However, conditions of high stringency are used only if the probes are complementary to regions of the chromosome which are unique in the genome. The stringency of hybridization is determined by a number of factors during hybridization and during the washing procedure, including temperature, ionic strength, base composition, probe length, and concentration of formamide. These factors are outlined in, for example, Maniatis et al., 1982 and Sambrook et al., 1989. Under certain circumstances, the formation of higher order hybrids, such as triplexes, quadraplexes, etc., may be desired to provide the means of detecting target sequences.

Detection, if any, of the resulting hybrid is usually accomplished by the use of labeled probes. Alternatively, the probe may be unlabeled, but may be detectable by specific binding with a ligand which is labeled, either directly or indirectly. Suitable labels, and methods for labeling probes and ligands are known in the art, and include, for example, radioactive labels which may be incorporated by known methods (e.g., nick translation, random priming or kinasing), biotin, fluorescent groups, chemiluminescent groups (e.g., dioxetanes, particularly triggered dioxetanes), enzymes, antibodies and the like. Variations of this basic scheme are known in the art, and include those variations that facilitate separation of the hybrids to be detected from extraneous materials and/or that amplify the signal from the labeled moiety. A number of these variations are reviewed in, e.g., Matthews & Kricka, 1988; Landegren et al., 1988; Mittlin, 1989; U.S. Pat. No. 4,868,105, and in EPO Publication No. 225,807.

As noted above, non-PCR based screening assays are also contemplated in this invention. An exemplary non-PCR based procedure is provided in Example 11. This procedure hybridizes a nucleic acid probe (or an analog such as a methyl phosphonate backbone replacing the normal phosphodiester), to the low level DNA target. This probe may have an enzyme covalently linked to the probe, such that the covalent linkage does not interfere with the specificity of the hybridization. This enzyme-probe-conjugate-target nucleic acid complex can then be isolated away from the free probe enzyme conjugate and a substrate is added for enzyme detection. Enzymatic activity is observed as a change in color development or luminescent output resulting in a 10^3–10^6 increase in sensitivity. For an example relating to the preparation of oligodeoxynucleotide-alkaline phosphatase conjugates and their use as hybridization probes see Jablonski et al., 1986.

Two-step label amplification methodologies are known in the art. These assays work on the principle that a small ligand (such as digoxigenin, biotin, or the like) is attached to a nucleic acid probe capable of specifically binding BRCA1. Exemplary probes are provided in Table 9 of this patent application and additionally include the nucleic acid probe corresponding to nucleotide positions 3631 to 3930 of SEQ ID NO: 1. Allele specific probes are also contemplated within the scope of this example and exemplary allele specific probes include probes encompassing the predisposing mutations summarized in Tables 11 and 12 of this patent application.

In one example, the small ligand attached to the nucleic acid probe is specifically recognized by an antibody-enzyme conjugate. In one embodiment of this example, digoxigenin is attached to the nucleic acid probe. Hybridization is detected by an antibody-alkaline phosphatase conjugate which turns over a chemiluminescent substrate. For methods for labeling nucleic acid probes according to this embodiment see Martin et al., 1990. In a second example, the small ligand is recognized by a second ligand-enzyme conjugate that is capable of specifically complexing to the first ligand. A well known embodiment of this example is the biotin-avidin type of interactions. For methods for labeling nucleic acid probes and their use in biotin-avidin based assays see Rigby et al., 1977 and Nguyen et al., 1992.

It is also contemplated within the scope of this invention that the nucleic acid probe assays of this invention will employ a cocktail of nucleic acid probes capable of detecting BRCA1. Thus, in one example to detect the presence of BRCA1 in a cell sample, more than one probe complementary to BRCA1 is employed and in particular the number of different probes is alternatively 2, 3, or 5 different nucleic acid probe sequences. In another example, to detect the presence of mutations in the BRCA1 gene sequence in a patient, more than one probe complementary to BRCA1 is employed where the cocktail includes probes capable of binding to the allele-specific mutations identified in populations of patients with alterations in BRCA1. In this embodiment, any number of probes can be used, and will preferably include probes corresponding to the major gene mutations identified as predisposing an individual to breast cancer. Some candidate probes contemplated within the scope of the invention include probes that include the allele-specific mutations identified in Tables 11 and 12 and those that have the BRCA1 regions corresponding to SEQ ID NO: 1 both 5' and 3' to the mutation site.

Methods of Use: Peptide Diagnosis and Diagnostic Kits

The neoplastic condition of lesions can also be detected on the basis of the alteration of wild-type BRCA1 polypeptide. Such alterations can be determined by sequence analysis in accordance with conventional techniques. More preferably, antibodies (polyclonal or monoclonal) are used to detect differences in, or the absence of BRCA1 peptides. The antibodies may be prepared as discussed above under the heading "Antibodies" and as further shown in Examples 12 and 13. Other techniques for raising and purifying antibodies are well known in the art and any such techniques may be chosen to achieve the preparations claimed in this invention. In a preferred embodiment of the invention, antibodies will immunoprecipitate BRCA1 proteins from solution as well as react with BRCA1 protein on Western or immunoblots of polyacrylamide gels. In another preferred embodiment, antibodies will detect BRCA1 proteins in paraffin or frozen tissue sections, using immunocytochemical techniques.

Preferred embodiments relating to methods for detecting BRCA1 or its mutations include enzyme linked immunosorbent assays (ELISA), radioimmunoassays (RIA), immunoradiometric assays (IRMA) and immunoenzymatic assays (IEMA), including sandwich assays using monoclonal and/or polyclonal antibodies. Exemplary sandwich assays are described by David et al. in U.S. Pat. Nos. 4,376,110 and 4,486,530, hereby incorporated by reference, and exemplified in Example 14.

Methods of Use: Drug Screening

This invention is particularly useful for screening compounds by using the BRCA1 polypeptide or binding fragment thereof in any of a variety of drug screening techniques.

The BRCA1 polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, or borne on a cell surface. One method of drug screening utilizes eucaryotic or procaryotic host cells which are stably transformed with recombinant polynucleotides expressing the polypeptide or fragment, preferably in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, for the formation of complexes between a BRCA1 polypeptide or fragment and the agent being tested, or examine the degree to which the formation of a complex between a BRCA1 polypeptide or fragment and a known ligand is interfered with by the agent being tested.

Thus, the present invention provides methods of screening for drugs comprising contacting such an agent with a BRCA1 polypeptide or fragment thereof and assaying (i) for the presence of a complex between the agent and the BRCA1 polypeptide or fragment, or (ii) for the presence of a complex between the BRCA1 polypeptide or fragment and a ligand, by methods well known in the art. In such competitive binding assays the BRCA1 polypeptide or fragment is typically labeled. Free BRCA1 polypeptide or fragment is separated from that present in a protein:protein complex, and the amount of free (i.e., uncomplexed) label is a measure of the binding of the agent being tested to BRCA1 or its interference with BRCA1:ligand binding, respectively.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the BRCA1 polypeptides and is described in detail in Geysen, PCT published application WO 84/03564, published on Sep. 13, 1984. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with BRCA1 polypeptide and washed. Bound BRCA1 polypeptide is then detected by methods well known in the art.

Purified BRCA1 can be coated directly onto plates for use in the aforementioned drug screening techniques. However, non-neutralizing antibodies to the polypeptide can be used to capture antibodies to immobilize the BRCA1 polypeptide on the solid phase.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of specifically binding the BRCA1 polypeptide compete with a test compound for binding to the BRCA1 polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants of the BRCA1 polypeptide.

A further technique for drug screening involves the use of host eukaryotic cell lines or cells (such as described above) which have a nonfunctional BRCA1 gene. These host cell lines or cells are defective at the BRCA1 polypeptide level. The host cell lines or cells are grown in the presence of drug compound. The rate of growth of the host cells is measured to determine if the compound is capable of regulating the growth of BRCA1 defective cells.

Methods of Use: Rational Drug Design

The goal of rational drug design is to produce structural analogs of biologically active polypeptides of interest or of small molecules with which they interact (e.g., agonists, antagonists, inhibitors) in order to fashion drugs which are, for example, more active or stable forms of the polypeptide, or which, e.g., enhance or interfere with the function of a polypeptide in vivo. See, e.g., Hodgson, 1991. In one approach, one first determines the three-dimensional structure of a protein of interest (e.g., BRCA1 polypeptide) or, for example, of the BRCA1-receptor or ligand complex, by x-ray crystallography, by computer modeling or most typically, by a combination of approaches. Less often, useful information regarding the structure of a polypeptide may be gained by modeling based on the structure of homologous proteins. An example of rational drug design is the development of HIV protease inhibitors (Erickson et al., 1990). In addition, peptides (e.g., BRCA1 polypeptide) are analyzed by an alanine scan (Wells, 1991). In this technique, an amino acid residue is replaced by Ala, and its effect on the peptide's activity is determined. Each of the amino acid residues of the peptide is analyzed in this manner to determine the important regions of the peptide.

It is also possible to isolate a target-specific antibody, selected by a functional assay, and then to solve its crystal structure. In principle, this approach yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idio-typic antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced banks of peptides. Selected peptides would then act as the pharmacore.

Thus, one may design drugs which have, e.g., improved BRCA1 polypeptide activity or stability or which act as inhibitors, agonists, antagonists, etc. of BRCA1 polypeptide activity. By virtue of the availability of cloned BRCA1 sequences, sufficient amounts of the BRCA1 polypeptide may be made available to perform such analytical studies as x-ray crystallography. In addition, the knowledge of the BRCA1 protein sequence provided herein will guide those employing computer modeling techniques in place of, or in addition to x-ray crystallography.

Methods of Use: Gene Therapy

According to the present invention, a method is also provided of supplying wild-type BRCA1 function to a cell which carries mutant BRCA1 alleles. Supplying such a function should suppress neoplastic growth of the recipient cells. The wild-type BRCA1 gene or a part of the gene may be introduced into the cell in a vector such that the gene remains extrachromosomal. In such a situation, the gene will be expressed by the cell from the extrachromosomal location. If a gene fragment is introduced and expressed in a cell carrying a mutant BRCA1 allele, the gene fragment should encode a part of the BRCA1 protein which is required for non-neoplastic growth of the cell. More preferred is the situation where the wild-type BRCA1 gene or a part thereof is introduced into the mutant cell in such a way that it recombines with the endogenous mutant BRCA1 gene present in the cell. Such recombination requires a double recombination event which results in the correction of the BRCA1 gene mutation. Vectors for introduction of genes both for recombination and for extrachromosomal maintenance are known in the art, and any suitable vector may be used. Methods for introducing DNA into cells such as electroporation, calcium phosphate co-precipitation and viral transduction are known in the art, and the choice of method is within the competence of the routineer. Cells transformed with the wild-type BRCA1 gene can be used as model systems to study cancer remission and drug treatments which promote such remission.

As generally discussed above, the BRCA1 gene or fragment, where applicable, may be employed in gene therapy methods in order to increase the amount of the expression products of such genes in cancer cells. Such gene therapy is particularly appropriate for use in both cancerous and pre-cancerous cells, in which the level of BRCA1 polypeptide is absent or diminished compared to normal cells. It may also be useful to increase the level of expression of a given BRCA1 gene even in those tumor cells in which the mutant gene is expressed at a "normal" level, but the gene product is not fully functional.

Gene therapy would be carrier out according to generally accepted methods, for example, as described by Friedman, 1991. Cells from a patient's tumor would be first analyzed by the diagnostic methods described above, to ascertain the production of BRCA1 polypeptide in the tumor cells. A virus or plasmid vector (see further details below), containing a copy of the BRCA1 gene linked to expression control elements and capable of replicating inside the tumor cells, is prepared. Suitable vectors are known, such as disclosed in U.S. Pat. No. 5,252,479 and PCT published application WO 93/07282. The vector is then injected into the patient, either locally at the site of the tumor or systemically (in order to reach any tumor cells that may have metastasized to other sites). If the transfected gene is not permanently incorporated into the genome of each of the targeted tumor cells, the treatment may have to be repeated periodically.

Gene transfer systems known in the art may be useful in the practice of the gene therapy methods of the present invention. These include viral and nonviral transfer methods. A number of viruses have been used as gene transfer vectors, including papovaviruses, e.g., SV40 (Madzak et al., 1992), adenovirus (Berkner, 1992; Berkner et al., 1988; Gorziglia and Kapikian, 1992; Quantin et al., 1992; Rosenfeld et al., 1992; Wilkinson et al., 1992; Stratford-Perricaudet et al., 1990), vaccinia virus (Moss, 1992), adeno-associated virus (Muzyczka, 1992; Ohi et al., 1990), herpesviruses including HSV and EBV (Margolskee, 1992; Johnson et al., 1992; Fink et al., 1992; Breakfield and Geller, 1987; Freese et al., 1990), and retroviruses of avian (Brandyopadhyay and Temin, 1984; Petropoulos et al., 1992), murine (Miller, 1992; Miller et al., 1985; Sorge et al., 1984; Mann and Baltimore, 1985; Miller et al., 1988), and human origin (Shimada et al., 1991; Helseth et al., 1990; Page et al., 1990; Buchschacher and Panganiban, 1992). Most human gene therapy protocols have been based on disabled murine retroviruses.

Nonviral gene transfer methods known in the art include chemical techniques such as calcium phosphate coprecipitation (Graham and van der Eb, 1973; Pellicer et al., 1980); mechanical techniques, for example microinjection (Anderson et al., 1980; Gordon et al., 1980; Brinster et al., 1981; Constantini and Lacy, 1981); membrane fusion-mediated transfer via liposomes (Felgner et al., 1987; Wang and Huang, 1989; Kaneda et al, 1989; Stewart et al., 1992; Nabel et al., 1990; Lim et al., 1992); and direct DNA uptake and receptor-mediated DNA transfer (Wolff et al., 1990; Wu et al., 1991; Zenke et al., 1990; Wu et al., 1989b; Wolff et al., 1991; Wagner et al., 1990; Wagner et al., 1991; Cotten et al., 1990; Curiel et al., 1991a; Curiel et al., 1991b). Viral-mediated gene transfer can be combined with direct in vivo gene transfer using liposome delivery, allowing one to direct the viral vectors to the tumor cells and not into the surrounding nondividing cells. Alternatively, the retroviral vector producer cell line can be injected into tumors (Culver et al., 1992). Injection of producer cells would then provide a continuous source of vector particles. This technique has been approved for use in humans with inoperable brain tumors.

In an approach which combines biological and physical gene transfer methods, plasmid DNA of any size is combined with a polylysine-conjugated antibody specific to the adenovirus hexon protein, and the resulting complex is bound to an adenovirus vector. The trimolecular complex is then used to infect cells. The adenovirus vector permits efficient binding, internalization, and degradation of the endosome before the coupled DNA is damaged.

Liposome/DNA complexes have been shown to be capable of mediating direct in vivo gene transfer. While in standard liposome preparations the gene transfer process is nonspecific, localized in vivo uptake and expression have been reported in tumor deposits, for example, following direct in situ administration (Nabel, 1992).

Gene transfer techniques which target DNA directly to breast and ovarian tissues, e.g., epithelial cells of the breast or ovaries, is preferred. Receptor-mediated gene transfer, for example, is accomplished by the conjugation of DNA (usually in the form of covalently closed supercoiled plasmid) to a protein ligand via polylysine. Ligands are chosen on the basis of the presence of the corresponding ligand receptors on the cell surface of the target cell/tissue type. One appropriate receptor/ligand pair may include the estrogen receptor and its ligand, estrogen (and estrogen analogues). These ligand-DNA conjugates can be injected directly into the blood if desired and are directed to the target tissue where receptor binding and internalization of the DNA-protein complex occurs. To overcome the problem of intracellular destruction of DNA, coinfection with adenovirus can be included to disrupt endosome function.

The therapy involves two steps which can be performed singly or jointly. In the first step, prepubescent females who carry a BRCA1 susceptibility allele are treated with a gene delivery vehicle such that some or all of their mammary ductal epithelial precursor cells receive at least one additional copy of a functional normal BRCA1 allele. In this step, the treated individuals have reduced risk of breast cancer to the extent that the effect of the susceptible allele has been countered by the presence of the normal allele. In the second step of a preventive therapy, predisposed young females, in particular women who have received the proposed gene therapeutic treatment, undergo hormonal therapy to mimic the effects on the breast of a full term pregnancy.

Methods of Use: Peptide Therapy

Peptides which have BRCA1 activity can be supplied to cells which carry mutant or missing BRCA1 alleles. The sequence of the BRCA1 protein is disclosed (SEQ ID NO:2). Protein can be produced by expression of the cDNA sequence in bacteria, for example, using known expression vectors. Alternatively, BRCA1 polypeptide can be extracted from BRCA1-producing mammalian cells. In addition, the techniques of synthetic chemistry can be employed to synthesize BRCA1 protein. Any of such techniques can provide the preparation of the present invention which comprises the BRCA1 protein. The preparation is substantially free of other human proteins. This is most readily accomplished by synthesis in a microorganism or in vitro.

Active BRCA1 molecules can be introduced into cells by microinjection or by use of liposomes, for example. Alternatively, some active molecules may be taken up by cells, actively or by diffusion. Extracellular application of the BRCA1 gene product may be sufficient to affect tumor growth. Supply of molecules with BRCA1 activity should lead to partial reversal of the neoplastic state. Other molecules with BRCA1 activity (for example, peptides, drugs or organic compounds) may also be used to effect such a reversal. Modified polypeptides having substantially similar function are also used for peptide therapy.

Methods of Use: Transformed Hosts

Similarly, cells and animals which carry a mutant BRCA1 allele can be used as model systems to study and test for substances which have potential as therapeutic agents. The cells are typically cultured epithelial cells. These may be isolated from individuals with BRCA1 mutations, either somatic or germline. Alternatively, the cell line can be engineered to carry the mutation in the BRCA1 allele, as described above. After a test substance is applied to the cells, the neoplastically transformed phenotype of the cell is determined. Any trait of neoplastically transformed cells can be assessed, including anchorage-independent growth, tumorigenicity in nude mice, invasiveness of cells, and growth factor dependence. Assays for each of these traits are known in the art.

Animals for testing therapeutic agents can be selected after mutagenesis of whole animals or after treatment of germline cells or zygotes. Such treatments include insertion of mutant BRCA1 alleles, usually from a second animal species, as well as insertion of disrupted homologous genes.

Alternatively, the endogenous BRCA1 gene(s) of the animals may be disrupted by insertion or deletion mutation or other genetic alterations using conventional techniques (Capecchi, 1989; Valancius and Smithies, 1991; Hasty et al., 1991; Shinkai et al., 1992; Mombaerts et al., 1992; Philpott et al., 1992; Snouwaert et al., 1992; Donehower et al., 1992). After test substances have been administered to the animals, the growth of tumors must be assessed. If the test substance prevents or suppresses the growth of tumors, then the test substance is a candidate therapeutic agent for the treatment of the cancers identified herein. These animal models provide an extremely important testing vehicle for potential therapeutic products.

The present invention is described by reference to the following Examples, which are offered by way of illustration and are not intended to limit the invention in any manner. Standard techniques well known in the art or the techniques specifically described below were utilized.

EXAMPLE 1

Ascertain and Study Kindreds Likely to Have a 17q-Linked Breast Cancer Susceptibility Locus

Extensive cancer prone kindreds were ascertained by our University of Utah Collaborators from a defined population providing a large set of extended kindreds with multiple cases of breast cancer and many relatives available to study. The large number of meioses present in these large kindreds provided the power to detect whether the BRCA1 locus was segregating, and increased the opportunity for informative recombinants to occur within the small region being investigated. This vastly improved the chances of establishing linkage to the BRCA1 region, and greatly facilitated the reduction of the BRCA1 region to a manageable size, which permits identification of the BRCA1 locus itself.

Each kindred was extended through all available connecting relatives by our collaborators, and to all informative first degree relatives of each proband or cancer case. For these kindreds, additional breast cancer cases and individuals with cancer at other sites of interest (e.g. ovarian) who also appeared in the kindreds were identified through the tumor registry linked files. All breast cancers reported in the kindred which were not confirmed in the Utah Cancer Registry were researched. Medical records or death certificates were obtained for confirmation of all cancers. Each key connecting individual and all informative individuals were invited by our collaborators to participate by providing a blood sample from which DNA was extracted. They also sampled spouses and relatives of deceased cases so that the genotype of the deceased cases could be inferred from the genotypes of their relatives.

Ten kindreds which had three or more cancer cases with inferable genotypes were selected for linkage studies to 17q markers from a set of 29 kindreds originally ascertained for a study of proliferative breast disease and breast cancer (Skolnick et al., 1990). The criterion for selection of these kindreds was the presence of two sisters or a mother and her daughter with breast cancer. Additionally, two kindreds which have been studied by our collaborators their since 1980 as part of our breast cancer linkage studies (K1001, K9018), six kindreds ascertained for the presence of clusters of breast and/or ovarian cancer (K2019, K2073, K2079, K2080, K2039, K2082) and a self-referred kindred with early onset breast cancer (K2035) were included. These kindreds were investigated and expanded in our collaborators clinic in the manner described above. Table 1 displays the characteristics of these 19 kindreds which are the subject of subsequent examples. In Table 1, for each kindred the total number of individuals in our database, the number of typed individuals, and the minimum, median, and maximum age at diagnosis of breast/ovarian cancer are reported. Kindreds are sorted in ascending order of median age at diagnosis of breast cancer. Four women diagnosed with both ovarian and breast cancer are counted in both categories.

TABLE 1

Description of the 19 Kindreds

	No. of Individuals		Breast				Ovarian			
				Age at Dx				Age at Dx		
KINDRED	Total	Sample	# Aff.	Min.	Med.	Max.	# Aff.	Min.	Med.	Max.
1910	15	10	4	27	34	49	—	—	—	—
1001	133	98	13	28	37	64	—	—	—	—
2035	42	25	8	28	37	45	1	—	60	—
2027	21	11	4	34	38	41	—	—	—	—
9018	54	17	9	30	40	72	2	46	48	50
1925	30	27	4	39	42	53	—	—	—	—
1927	49	29	5	32	42	51	—	—	—	—
1911	28	21	7	28	42	76	—	—	—	—
1929	16	11	4	34	43	73	—	—	—	—
1901	35	19	10	31	44	76	—	—	—	—
2082	180	105	20	27	47	67	10	45	52	66
2019	42	19	10	42	53	79	—	—	—	—
1900	70	23	8	45	55	70	1	—	78	—
2080	264	74	22+	27	55	92	4	45	53	71
2073	57	29	9	35	57	80	—	—	—	—
1917	16	6	4	43	58	61	—	—	—	—
1920	22	14	3	62	63	68	—	—	—	—
2079	136	18	14	38	66	84	4	52	59	63
2039	87	40	14	44	68	88	4	41	51	75

+Includes one case of male breast cancer

EXAMPLE 2

Selection of Kindreds Which are Linked to Chromosome 17q and Localization of BRCA1 to the Interval Mfd15–Mfd188

For each sample collected in these 19 kindreds, DNA was extracted from blood (or in two cases from paraffin-embedded tissue blocks) using standard laboratory protocols. Genotyping in this study was restricted to short tandem repeat (STR) markers since, in general, they have high heterozygosity and PCR methods offer rapid turnaround while using very small amounts of DNA. To aid in this effort, four such STR markers on chromosome 17 were developed by screening a chromosome specific cosmid library for CA positive clones. Three of these markers localized to the long arm: (46E6, Easton et al., 1993); (42D6, Easton et al., 1993); 26C2 (D17S514, Oliphant et al., 1991), while the other, 12G6 (D17S513, Oliphant et al., 1991), localized to the short arm near the p53 tumor suppressor locus. Two of these, 42D6 and 46E6, were submitted to the Breast Cancer Linkage Consortium for typing of breast cancer families by investigators worldwide. Oligonucleotide sequences for markers not developed in our laboratory were obtained from published reports, or as part of the Breast Cancer Linkage Consortium, or from other investigators. All genotyping films were scored blindly with a standard lane marker used to maintain consistent coding of alleles. Key samples in the four kindreds presented here underwent duplicate typing for all relevant markers. All 19 kindreds have been typed for two polymorphic CA repeat markers: 42D6 (D17S588), a CA repeat isolated in our laboratory, and Mfd15 (D17S250), a CA repeat provided by J. Weber (Weber et al., 1990). Several sources of probes were used to create genetic markers on chromosome 17, specifically chromosome 17 cosmid and lambda phage libraries created from sorted chromosomes by the Los Alamos National Laboratories (van Dilla et al., 1986).

LOD scores for each kindred with these two markers (42D6, Mfd15) and a third marker, Mfd188 (D17S579, Hall et al., 1992), located roughly midway between these two markers, were calculated for two values of the recombination fraction, 0.001 and 0.1. (For calculation of LOD scores, see Oh, 1985). Likelihoods were computed under the model derived by Claus et al., 1991, which assumes an estimated gene frequency of 0.003, a lifetime risk in gene carriers of about 0.80, and population based age-specific risks for breast cancer in non-gene carriers. Allele frequencies for the three markers used for the LOD score calculations were calculated from our own laboratory typings of unrelated individuals in the CEPH panel (White and Lalouel, 1988). Table 2 shows the results of the pairwise linkage analysis of each kindred with the three markers 42D6, Mfd188, and Mfd15.

TABLE 2

Pairwise Linkage Analysis of Kindreds

	Mfd15 (D17S250) Recombination		Mfd188 (D17S579) Recombination		42D6 (D17S588) Recombination	
KINDRED	0.001	0.1	0.001	0.1	0.001	0.1
1910	0.06	0.30	0.06	0.30	0.06	0.30
1001	−0.30	−0.09	NT	NT	−0.52	−0.19
2035	2.34	1.85	0.94	0.90	2.34	1.82
2027	−1.22	−0.33	−1.20	−0.42	−1.16	−0.33
9018	−0.54	−0.22	−0.17	−0.10	0.11	0.07
1923	1.08	0.79	0.55	0.38	−0.11	−0.07
1927	−0.41	0.01	−0.35	0.07	−0.44	−0.02
1911	−0.27	−0.13	−0.43	−0.23	0.49	0.38
1929	−0.49	−0.25	NT	NT	−0.49	−0.25
1901	1.50	1.17	0.78	0.57	0.65	0.37
2082	4.25	3.36	6.07	5.11	2.00	3.56
2019	−0.10	−0.01	−0.11	−0.05	−0.18	−0.10
1900	−0.14	−0.11	NT	NT	−0.12	−0.05

TABLE 2-continued

Pairwise Linkage Analysis of Kindreds

	Mfd15 (D17S250) Recombination		Mfd188 (D17S579) Recombination		42D6 (D17S588) Recombination	
KINDRED	0.001	0.1	0.001	0.1	0.001	0.1
2080	−0.16	−0.04	0.76	0.74	−1.25	−0.58
2073	−0.41	−0.29	0.63	0.49	−0.23	−0.13
1917	−0.02	−0.02	NT	NT	−0.01	0.00
1920	−0.03	−0.02	NT	NT	0.00	0.00
2079	0.02	0.01	−0.01	−0.01	0.01	0.01
2039	−1.67	−0.83	0.12	0.59	−1.15	0.02

NT - Kindred not typed for Mfd188.

Using a criterion for linkage to 17q of a LOD score >1.0 for at least one locus under the CASH model (Claus et al., 1991), four of the 19 kindreds appeared to be linked to 17q (K1901, K1925, K2035, K2082). A number of additional kindreds showed some evidence of linkage but at this time could not be definitively assigned to the linked category. These included kindreds K1911, K2073, K2039, and K2080. Three of the 17q-linked kindreds had informative recombinants in this region and these are detailed below.

Kindred 2082 is the largest 17q-linked breast cancer family reported to date by any group. The kindred contains 20 cases of breast cancer, and ten cases of ovarian cancer. Two cases have both ovarian and breast cancer. The evidence of linkage to 17q for this family is overwhelming; the LOD score with the linked haplotype is over 6.0, despite the existence of three cases of breast cancer which appear to be sporadic, i.e., these cases share no part of the linked haplotype between Mfd5 and 42D6. These three sporadic cases were diagnosed with breast cancer at ages 46, 47, and 54. In smaller kindreds, sporadic cancers of this type greatly confound the analysis of linkage and the correct identification of key recombinants. The key recombinant in the 2082 kindred is a woman who developed ovarian cancer at age 45 whose mother and aunt had ovarian cancer at ages 58 and 66, respectively. She inherited the linked portion of the haplotype for both Mfd188 and 42D6 while inheriting unlinked alleles at Mfd5; this recombinant event placed BRCA1 distal to Mfd5.

K1901 is typical of early-onset breast cancer kindreds. The kindred contains 10 cases of breast cancer with a median age at diagnosis of 43.5 years of age; four cases were diagnosed under age 40. The LOD score for this kindred with the marker 42D6 is 1.5, resulting in a posterior probability of 17q-linkage of 0.96. Examination of haplotypes in this kindred identified a recombinant haplotype in an obligate male carrier and his affected daughter who was diagnosed with breast cancer at age 45. Their linked allele for marker Mfd15 differs from that found in all other cases in the kindred (except one case which could not be completely inferred from her children). The two haplotypes are identical for Mfd188 and 42D6. Accordingly, data from Kindred 1901 would also place the BRCA1 locus distal to Mfd15.

Kindred 2035 is similar to K1901 in disease phenotype. The median age of diagnosis for the eight cases of breast cancer in this kindred is 37. One case also had ovarian cancer at age 60. The breast cancer cases in this family descend from two sisters who were both unaffected with breast cancer until their death in the eighth decade. Each branch contains four cases of breast cancer with at least one case in each branch having markedly early onset. This kindred has a LOD score of 2.34 with Mfd15. The haplotypes segregating with breast cancer in the two branches share an identical allele at Mfd15 but differ for the distal loci Mfd188 and NM23 (a marker typed as part of the consortium which is located just distal to 42D6 (Hall et al., 1992)). Although the two haplotypes are concordant for marker 42D6, it is likely that the alleles are shared identical by state (the same allele but derived from different ancestors), rather than identical by descent (derived from a common ancestor) since the shared allele is the second most common allele observed at this locus. By contrast the linked allele shared at Mfd15 has a frequency of 0.04. This is a key recombinant in our dataset as it is the sole recombinant in which BRCA1 segregated with the proximal portion of the haplotype, thus setting the distal boundary to the BRCA1 region. For this event not to be a key recombinant requires that a second mutant BRCA1 gene be present in a spouse marrying into the kindred who also shares the rare Mfd15 allele segregating with breast cancer in both branches of the kindred. This event has a probability of less than one in a thousand. The evidence from this kindred therefore placed the BRCA1 locus proximal to Mfd188.

Genetic localization of markers. In order to localize new markers genetically within the region of interest, we have identified a number of key meiotic breakpoints within the region, both in the CEPH reference panel and in our large breast cancer kindred (K2082). Given the small genetic distance in this region, they are likely to be only a relatively small set of recombinants which can be used for this purpose, and they are likely to group markers into sets. The orders of the markers within each set can only be determined by physical mapping. However the number of genotypings necessary to position a new marker is minimized. These breakpoints are illustrated in Tables 3 and 4. Using this approach we were able to genetically order the markers THRA1, 6C1, SCG40, and Mfd191. As can be seen from Tables 3 and 4, THRA1 and MFD191 both map inside the Mfd15–Mfd188 region we had previously identified as containing the BRCA1 locus. In Tables 3 and 4, M/P indicates a maternal or paternal recombinant. A "1" indicates inherited allele is of grandpaternal origin, while a "0" indicates grandmaternal origin, and "-" indicates that the locus was untyped or uninformative.

TABLE 3

CEPH Recombinants

Family	ID	M/P	Mfd15	THRA1	Mfd191	Mfd188	SCG40	6C1	42D6
13292	4	M	1	1	1	0	0	0	0
13294	4	M	1	1	1	0	0	0	0
13294	6	M	0	0	1	1	—	—	—
1334	3	M	1	1	1	1	1	0	0
1333	4	M	1	1	1	0	—	—	0
1333	6	M	0	0	1	1	—	—	1
1333	8	P	1	0	0	0	—	—	0
1377	8	M	0	—	0	0	0	0	1

EXAMPLE 3

Creation of a Fine Structure Map and Refinement of the BRCA1 Region to Mfd191–Mfd188 using Additional STR Polymorphisms

In order to improve the characterization of our recombinants and define closer flanking markers, a dense map of this relatively small region on chromosome 17q was required. The chromosome 17 workshop has produced a consensus map of this region (FIG. 1) based on a combination of genetic and physical mapping studies (Fain, 1992). This map contains both highly polymorphic STR polymorphisms, and a number of nonpolymorphic expressed genes. Because this map did not give details on the evidence for this order nor give any measure of local support for inversions in the order of adjacent loci, we viewed it as a rough guide for obtaining resources to be used for the development of new markers and construction of our own detailed genetic and physical map of a small region containing BRCA1. Our approach was to analyze exand ag STR markers provided by other investigators and any newly developed markers from our laboratory with respect to both a panel of meiotic (genetic) breakpoints identified using DNA from the CEPH reference families and a panel of somatic cell hybrids (physical breakpoints) constructed for this region. These markers included 26C2 developed in our laboratory which maps proximal to Mfd15, Mfd191 (provided by James Weber), THRA1 (Futreal et al., 1992a), and three polymorphisms kindly provided to us by Dr. Donald Black, NM23 (Hall et al. 1992), SCG40 (D17S181), and 6C1 (D17S293).

TABLE 4

Kindred 2082 Recombinants

Family	ID	M/P	Mfd15	Mfd191	Mfd188	SCG40	6C1	42D6
75		M	0	1	1	1	—	—
63		M	0	0	1	1	—	1
125		M	1	1	1	0	—	0
40		M	1	1	0	0	—	0

Analysis of markers Mfd15, Mfd188, Mfd191, and THRA 1 in our recombinant families. Mfd15, Mfd188, Mfd191 and THRA1 were typed in our recombinant families and examined for additional information to localize the BRCA1 locus. In kindred 1901, the Mfd15 recombinant was recombinant for THRA1 but uninformative for Mfd191, thus placing BRCA1 distal to THRA1. In K2082, the recombinant with Mfd15 also was recombinant with Mfd191, thus placing the BRCA1 locus distal to Mfd191 (Goldgar et al., 1994). Examination of THRA1 and Mfd191 in kindred K2035 yielded no further localization information as the two branches were concordant for both markers. However, SCG40 and 6C1 both displayed the same pattern as Mfd188, thus increasing our confidence in the localization information provided by the Mfd188 recombinant in this family. The BRCA1 locus, or at least a portion of it, therefore lies within an interval bounded by Mfd191 on the proximal side and Mfd188 on the distal side.

EXAMPLE 4

Development of Genetic and Physical Resources in the Region of Interest

To increase the number of highly polymorphic loci in the Mfd191–Mfd188 region, we developed a number of STR markers in our laboratory from cosmids and YACs which physically map to the region. These markers allowed us to further refine the region.

STSs were identified from genes known to be in the desired region to identify YACs which contained these loci, which were then used to identify subclones in cosmids, P1s or BACs. These subclones were then screened for the presence of a CA tandem repeat using a $(CA)_n$ oligonucleotide (Pharmacia). Clones with a strong signal were selected preferentially, since they were more likely to represent CA-repeats which have a large number of repeats and/or are of near-perfect fidelity to the $(CA)_n$ pattern. Both of these characteristics are known to increase the probability of polymorphism (Weber, 1990). These clones were sequenced directly from the vector to locate the repeat. We obtained a unique sequence on one side of the CA-repeat by using one of a set of possible primers complementary to the end of a CA-repeat, such as $(GT)_{10}T$. Based on this unique sequence, a primer was made to sequence back across the repeat in the other direction, yielding a unique sequence for design of a second primer flanking the CA-repeat. STRs were then screened for polymorphism on a small group of unrelated individuals and tested against the hybrid panel to confirm their physical localization. New markers which satisfied these criteria were then typed in a set of 40 unrelated individuals from the Utah and CEPH families to obtain allele frequencies appropriate for the study population. Many of the other markers reported in this study were tested in a smaller group of CEPH unrelated individuals to obtain similarly appropriate allele frequencies.

Using the procedure described above, a total of eight polymorphic STRs was found from these YACS. Of the loci identified in this manner, four were both polymorphic and localized to the BRCA1 region. Four markers did not localize to chromosome 17, reflecting the chimeric nature of the YACs used. The four markers which were in the region were denoted AA1, ED2, 4–7, and YM29. AA1 and ED2 were developed from YACs positive for the RNU2 gene, 4–7 from an EPB3 YAC and YM29 from a cosmid which localized to the region by the hybrid panel. A description of the number of alleles, heterozygosity and source of these four and all other STR polymorphisms analyzed in the breast cancer kindreds is given below in Table 5.

TABLE 5

Polymorphic Short Tandem Repeat Markers Used for Fine Structure Mapping of the BRCA1 Locus

Clone	Gene	Na**	Hetero-zygosity	Allele* Frequency (%) 1	2	3	4	5	6
Mfd15	D17S250	10	0.82	26	22	13	7	7	23
THRA1	THRA1	5							
Mfd191	D17S776	7	0.55	48	20	11	7	7	7
ED2	D17S1327	12	0.55	62	9	8	5	5	11
AA1	D17S1326	7	0.83	28	28	25	8	6	5
CA375	D17S184	10	0.75	26	15	11	9	9	20
4–7	D17S1183	9	0.50	63	15	8	6	4	4
YM29	—	9	0.62	42	24	12	7	7	8
Mfd188	D17S579	12	0.92	33	18	8	8	8	25
SCG40	D17S181	14	0.90	20	18	18	10	8	35
42D6	D17S588	11	0.86	21	17	11	10	9	32
6C1	D17S293	7	0.75	30	30	11	11	9	9
Z109	D17S750	9	0.70	33	27	7	7	7	19
tdj1475	D17S1321	13	0.84	21	16	11	11	8	33
CF4	D17S1320	6	0.63	50	27	9	7	4	3
tdj1239	D17S1328	10	0.80	86	10	9	7	4	14
U5	D17S1325	13	0.83	19	16	12	10	9	34

*Allele codes 1–5 are listed in decreasing frequency; allele numbers do not correspond to fragment sizes. Allele 6 frequency is the joint frequency of all other alleles for each locus.

**Number of alleles seen in the genetically independent DNA samples used for calculating allele frequencies.

The four STR polymorphisms which mapped physically to the region (4–7, ED2, AA1, YM29) were analyzed in the meiotic, breakpoint panel shown initially in Tables 3 and 4. Tables 6 and 7 contain the relevant CEPH data and Kindred 2082 data for localization of these four markers. In the tables, M/P indicates a maternal or paternal recombinant. A "1" indicates inherited allele is of grandpaternal origin, while a "0" indicates grandmaternal origin, and "-" indicates that the locus was untyped or uninformative.

TABLE 6

Key Recombinants Used for Genetic Ordering of New STR Loci Developed in Our Laboratory Within the BRCA1 Region of 17q

CEPH Family	ID	M/P	Mfd15	THRA1	Mfd191	ED2	AA1	Z109	4-7	YM29	Mfd188	SCG40	42D6
13292	4	M	1	1	1	1	1	0	0	0	0	0	0
13294	4	M	1	0	0	—	0	—	—	—	0	—	—
13294	6	M	0	0	1	—	1	—	—	—	1	—	—
1333	4	M	1	1	1	—	0	—	—	0	0	—	0
1333	6	M	0	0	1	—	1	—	—	1	1	—	1
1333	3	M	0	0	1	—	—	—	1	1	1	—	1

TABLE 7

Kindred 2082 Recombinants										
ID	M/P	Mfd15	Mfd191	ED2	AA1	4–7	YM29	Mfd188	SCG40	42D6
63	M	0	0	1	—	1	1	1	1	1
125	M	1	1	1	—	1	1	1	0	0
40	M	1	1	0	—	0	—	0	0	0
22	P	0	0	1	1	1	1	1	1	1

From CEPH 1333-04, we see that AA1 and YM29 must lie distal to Mfd191. From 13292, it can be inferred that both AA1 and ED2 are proximal to 4–7, YM29, and Mfd188. The recombinants found in K2082 provide some additional ordering information. Three independent observations (individual numbers 22, 40, & 63) place AA1, ED2, 4–7, and YM29, and Mfd188 distal to Mfd191, while ID 125 places 4–7, YM29, and Mfd188 proximal to SCG40. No genetic information on the relative ordering within the two clusters of markers AA1/ED2 and 4–7/YM29/Mfd188 was obtained from the genetic recombinant analysis. Although ordering loci with respect to hybrids which are known to contain "holes" in which small pieces of interstitial human DNA may be missing is problematic, the hybrid patterns indicate that 4–7 lies above both YM29 and Mfd188.

EXAMPLE 5

Genetic Analyses of Breast Cancer Kindreds with Markers AA1, 4–7, ED2, and YM29

In addition to the three kindreds containing key recombinants which have been discussed previously, kindred K2039 was shown through analysis of the newly developed STR markers to be linked to the region and to contain a useful recombinant.

Table 8 defines the haplotypes (shown in coded form) of the kindreds in terms of specific marker alleles at each locus and their respective frequencies. In Table 8, alleles are listed in descending order of frequency; frequencies of alleles 1–5 for each locus are given in Table 5. Haplotypes coded H are BRCA1 associated haplotypes. P designates a partial H haplotype, and an R indicates an observable recombinant haplotype. As evident in Table 8, not all kindreds were typed for all markers; moreover, not all individuals within a kindred were typed for an identical set of markers, especially in K2082. With one exception, only haplotypes inherited from affected or at-risk kindred members are shown; haplotypes from spouses marrying into the kindred are not described. Thus in a given sibship, the appearance of haplotypes X and Y indicates that both haplotypes from the affected/at-risk individual were seen and neither was a breast cancer associated haplotype.

TABLE 8

Breast Cancer Linked Haplotypes Found in the Three Kindreds

Kin.	HAP	Mfd 15	THRA1	Mfd 191	tdj 1475	ED2	AA1	Z109	CA375	4-7	YM29	Mfd 188	SCG40	6C1	42D6
1901	H1	1	5	5	3	1	4	NI	NI	1	1	3	NI	NI	1
	R2	9	2	5	6	1	4	NI	NI	1	1	3	NI	NI	1
2082	H1	3	NI	4	6	6	1	NI	NI	2	1	4	2	NI	1
	P1	3	NI	4	NI	NI	NI	NI	NI	NI	NI	4	2	NI	1
	P2	3	NI	NI	NI	NI	NI	NI	NI	NI	NI	4	NI	NI	NI
	R1	6	NI	1	5	6	1	NI	NI	2	1	4	2	NI	1
	R2	6	NI	4	6	6	1	NI	NI	2	1	4	2	NI	1
	R3	3	NI	4	NI	6	1	NI	NI	2	1	4	1	NI	7
	R4	7	NI	1	NI	1	5	NI	NI	4	6	1	2	NI	1
	R5	3	NI	4	NI	NI	NI	NI	NI	NI	2	1	NI	NI	NI
	R6	3	NI	4	3	1	2	NI	NI	1	2	2	6	NI	6
	R7	3	NI	4	3	7	1	NI	NI	1	1	3	7	NI	4
2035	H1	8	2	1	NI	5	1	1	4	3	1	6	8	2	4
	H2	8	2	1	NI	5	1	1	2	1	1	2	3	1	4
	R2	8	2	1	NI	5	1	1	2	1	1	2	3	6	1

In kindred K1901, the new markers showed no observable recombination with breast cancer susceptibility, indicating that the recombination event in this kindred most likely took place between THRA1 and ED2. Thus, no new BRCA1 localization information was obtained based upon studying the four new markers in this kindred. In kindred 2082 the key recombinant individual has inherited the linked alleles for ED2, 4–7, AA1, and YM29, and was recombinant for tdj1474 indicating that the recombination event occurred in this individual between tdj1474 and ED2/AA1.

There are three haplotypes of interest in kindred K2035, H1, H2, and R2 shown in Table 8. H1 is present in the four cases and one obligate male carrier descendant from individual 17 while H2 is present or inferred in two cases and two obligate male carriers in descendants of individual 10. R2 is identical to H2 for loci between and including Mfd15 and SCG40, but has recombined between SCG40 and 42D6. Since we have established that BRCA1 is proximal to 42D6, this H2/R2 difference adds no further localization information. H1 and R2 share an identical allele at Mfd15, THRA1, AA1, and ED2 but differ for loci presumed distal to ED2, i.e., 4–7, Mfd188, SCG40, and 6C1. Although the two haplotypes are concordant for the 5th allele for marker YM29, a marker which maps physically between 4–7 and Mfd188, it is likely that the alleles are shared identical by state rather than identical by descent since this allele is the most common allele at this locus with a frequency estimated in CEPH parents of 0.42. By contrast, the linked alleles shared at the Mfd15 and ED2 loci have frequencies of 0.04 and 0.09, respectively. They also share more common alleles at Mfd191 (frequency=0.52), THRA1, and AA1 (frequency=0.28). This is the key recombinant in the set as it is the sole recombinant in which breast cancer segregated with the proximal portion of the haplotype, thus setting the distal boundary. The evidence from this kindred therefore places the BRCA1 locus proximal to 4–7.

The recombination event in kindred 2082 which places BRCA1 distal to tdj1474 is the only one of the four events described which can be directly inferred; that is, the affected mother's genotype can be inferred from her spouse and offspring, and the recombinant haplotype can be seen in her affected daughter. In this family the odds in favor of affected individuals carrying BRCA1 susceptibility alleles are extremely high; the only possible interpretations of the data are that BRCA1 is distal to Mfd191 or alternatively that the purported recombinant is a sporadic case of ovarian cancer at age 44. Rather than a directly observable or inferred recombinant, interpretation of kindred 2035 depends on the observation of distinct 17q-haplotypes segregating in different and sometimes distantly related branches of the kindred. The observation that portions of these haplotypes have alleles in common for some markers while they differ at other markers places the BRCA1 locus in the shared region. The confidence in this placement depends on several factors: the relationship between the individuals carrying the respective haplotypes, the frequency of the shared allele, the certainty with which the haplotypes can be shown to segregate with the BRCA1 locus, and the density of the markers in the region which define the haplotype. In the case of kindred 2035, the two branches are closely related, and each branch has a number of early onset cases which carry the respective haplotype. While two of the shared alleles are common, (Mfd191, THRA1), the estimated frequencies of the shared alleles at Mfd15, AA1, and ED2 are 0.04, 0.28, and 0.09, respectively. It is therefore highly likely that these alleles are identical by descent (derived from a common ancestor) rather than identical by state (the same allele but derived from the general population).

EXAMPLE 6

Refined Physical Mapping Studies Place the BRCA1 Gene in a Region Flanked by tdj1474 and U5R

Since its initial localization to chromosome 17q in 1990 (Hall et al., 1990) a great deal of effort has gone into localizing the BRCA1 gene to a region small enough to allow implementation of effective positional cloning strategies to isolate the gene. The BRCA1 locus was first localized to the interval Mfd15 (D17S250)-42D6 (D17S588) by multipoint linkage analysis (Easton et al., 1993) in the collaborative Breast Cancer Linkage Consortium dataset consisting of 214 families collected worldwide. Subsequent refinements of the localization have been based upon individual recombinant events in specific families. The region THRA1-D17S183 was defined by Bowcock et al., 1993; and the region THRA1-D17S78 was defined by Simard et al., 1993.

We further showed that the BRCA1 locus must lie distal to the marker Mfd191 (D17S776) (Goldgar et al., 1994). This marker is known to lie distal to THRA1 and RARA. The smallest published region for the BRCA1 locus is thus between D17S776 and D17S78. This region still contains approximately 1.5 million bases of DNA, making the isolation and testing of all genes in the region a very difficult task. We have therefore undertaken the tasks of constructing a physical map of the region, isolating a set of polymorphic STR markers located in the region, and analyzing these new markers in a set of informative families to refine the location of the BRCA1 gene to a manageable interval.

Four families provide important genetic evidence for localization of BRCA1 to a sufficiently small region for the application of positional cloning strategies. Two families (K2082, K1901) provide data relating to the proximal boundary for BRCA1 and the other two (K2035, K1813) fix the distal boundary. These families are discussed in detail below. A total of 15 Short Tandem Repeat markers assayable by PCR were used to refine this localization in the families studied. These markers include DS17S7654, DS17S975, tdj1474, and tdj1239. Primer sequences for these markers are provided in SEQ ID NO:3 and SEQ ID NO:4 for DS17S754; in SEQ ID NO:5 and SEQ ID NO:6 for DS17S975; in SEQ ID NO:7 and SEQ ID NO:8 for tdj1474; and, in SEQ ID NO:9 and SEQ ID NO:10 for tdj1239.

Kindred 2082

Kindred 2082 is the largest BRCA1-linked breast/ovarian cancer family studied to date. It has a LOD score of 8.6, providing unequivocal evidence for 17q linkage. This family has been previously described and shown to contain a critical recombinant placing BRCA1 distal to MFD191 (D17S776). This recombinant occurred in a woman diagnosed with ovarian cancer at age 45 whose mother had ovarian cancer at age 63. The affected mother was deceased; however, from her children, she could be inferred to have the linked haplotype present in the 30 other linked cases in the family in the region between Mfd15 and Mfd188. Her affected daughter received the linked allele at the loci ED2, 4–7, and Mfd188, but received the allele on the non-BRCA1 chromosome at Mfd15 and Mfd191. In order to further localize this recombination breakpoint, we tested DNA from the key members of this family for the following markers derived from physical mapping resources: tdj1474, tdj1239, CF4, D17S855. For the markers tdj1474 and CF4, the affected daughter did not receive the linked allele. For the STR locus tdj1239, however, the mother could be inferred to be informative and her daughter did receive the BRCA1-associated allele. D17S855 was not informative in this family. Based on this analysis, the order is 17q centromere-Mfd191-17HSD-CF4-tdj1474-tdj1239-D17S855-ED2-4–7-Mfd188-17q telomere. The recombinant described above therefore places BRCA1 distal to tdj1474, and the breakpoint is localized to the interval between tdj1474 and tdj1239. The only alternative explanation for the data in this family other than that of BRCA1 being located distal to tdj1474, is that the ovarian cancer present in the recombinant individual is caused by reasons independent of the BRCA1 gene. Given that ovarian cancer diagnosed before age 50 is rare, this alternate explanation is exceedingly unlikely.

Kindred 1901

Kindred 1901 is an early-onset breast cancer family with 7 cases of breast cancer diagnosed before 50, 4 of which were diagnosed before age 40. In addition, there were three cases of breast cancer diagnosed between the ages of 50 and 70. One case of breast cancer also had ovarian cancer at age 61. This family currently has a LOD score of 1.5 with D17S855. Given this linkage evidence and the presence of at lease one ovarian cancer case, this family has a posterior probability of being due to BRCA1 of over 0.99. In this family, the recombination comes from the fact that an individual who is the brother of the ovarian cancer case from which the majority of the other cases descend, only shares a portion of the haplotype which is cosegregating with the other cases in the family. However, he passed this partial haplotype to his daughter who developed breast cancer at age 44. If this case is due to the BRCA1 gene, then only the part of the haplotype shared between this brother and his sister can contain the BRCA1 gene. The difficulty in interpretation of this kind of information is that while one can be sure of the markers which are not shared and therefore recombinant, markers which are concordant can either be shared because they are non-recombinant, or because their parent was homozygous. Without the parental genotypic data it is impossible to discriminate between these alternatives. Inspection of the haplotype in K1901, shows that he does not share the linked allele at Mfd15 (D17S250), THRA1, CF4 (D17S1320), and tdj1474 (17DS1321). He does share the linked allele at Mfd191 (D17S776), ED2 (D17S1327), tdj1239 (D17S1328), and Mfd188 (D17S579). Although the allele shared at Mfd191 is relatively rare (0.07), we would presume that the parent was homozygous since they are recombinant with markers located nearby on either side, and a double recombination event in this region would be extremely unlikely. Thus the evidence in this family would also place the BRCA1 locus distal to tdj1474. However, the lower limit of this breakpoint is impossible to determine without parental genotype information. It is intriguing that the key recombinant breakpoint in this family confirms the result in Kindred 2082. As before, the localization information in this family is only meaningful if the breast cancer was due to the BRCA1 gene. However, her relatively early age at diagnosis (44) makes this seem very likely since the risk of breast cancer before age 45 in the general population is low (approximately 1%).

Kindred 2035

This family is similar to K1901 in that the information on the critical recombinant events is not directly observed but is inferred from the observation that the two haplotypes which are cosegregating with the early onset breast cancer in the two branches of the family appear identical for markers located in the proximal portion of the 17q BRCA1 region but differ at more distal loci. Each of these two haplotypes occurs in at least four cases of early-onset or bilateral breast cancer. The overall LOD score with ED2 in this family is 2.2, and considering that there is a case of ovarian cancer in the family (indicating a prior probability of BRCA1 linkage of 80%), the resulting posterior probability that this family is linked to BRCA1 is 0.998. The haplotypes are identical for the markers Mfd15, THRA1, Mfd191, ED2, AA1, D17S858 and D17S902. The common allele at Mfd15 and ED2 are both quite rare, indicating that this haplotype is shared identical by descent. The haplotypes are discordant, however, for CA375, 4–7, and Mfd188, and several more distal markers. This indicates that the BRCA1 locus must lie above the marker CA-375. This marker is located approximately 50 kb below D17S78, so it serves primarily as additional confirmation of this previous lower boundary as reported in Simard et al. (1993).

Kindred 1813

Kindred 1813 is a small family with four cases of breast cancer diagnosed at very early ages whose mother also had breast cancer diagnosed at an early age and ovarian cancer some years later This family yields a maximum multipoint LOD score of 0.60 with 17q markers and, given that there is at least one case of ovarian cancer, results in a posterior probability of being a BRCA1 linked family of 0.93. This family contains a directly observable recombination event in individual 18 (see FIG. 5 in Simard et al., *Human Mol. Genet.* 2:1193–1199 (1993)), who developed breast cancer at age 34. The genotype of her affected mother at the relevant 17q loci can be inferred from her genotypes, her affected sister's genotypes, and the genotypes of three other unaffected siblings. Individual 18 inherits the BRCA1-linked alleles for the following loci: Mfd15, THRA1, D17S800, D17S855, AA1, and D17S931. However, for maker below D17S931, i.e., U5R, vrs31, D17S858, and D17S579, she has inherited the alleles locate non-disease bearing chromosome. The evidence from this family therefore would place the BRCA1 locus proximal to the marker U5R. Because of her early age at diagnosis (34) it is extremely unlikely that the recombinant individual's cancer is not due to the gene responsible for the other cases of breast/ovarian cancer in this family; the uncertainty in this family comes from our somewhat smaller amount of evidence that breast cancer in this family is due to BRCA1 rather than a second, as yet unmapped, breast cancer susceptibility locus.

Size of the region containing BRCA1

Based on the genetic data described in detail above, the BRCA1 locus must lie in the interval between the markers tdj1474 and U5R, both of which were isolated in our laboratory. Based upon the physical maps shown in FIGS. 2 and 3, we can try to estimate the physical distance between these two loci. It takes approximately 14 P1 clones with an average insert size of approximately 80 kb to span the region. However, because all of these P1s overlap to some unknown degree, the physical region is most likely much smaller than 14 times 80 kb. Based on restriction maps of the clones covering the region, we estimate the size of the region containing BRCA1 to be approximately 650 kb.

EXAMPLE 7

Identification of Candidate cDNA Clones for the BRCA1 Locus by Genomic Analysis of the Contig Region

Complete screen of the plausible region. The first method to identify candidate cDNAs, although labor intensive, used known techniques. The method comprised the screening of cosmids and P1 and BAC clones in the contig to identify putative coding sequences. The clones containing putative coding sequences were then used as probes on filters of cDNA libraries to identify candidate cDNA clones for future analysis. The clones were screened for putative coding sequences by either of two methods.

Zoo blots. The first method for identifying putative coding sequences was by screening the cosmid and P1 clones for sequences conserved through evolution across several species. This technique is referred to as "zoo blot analysis" and is described by Monaco, 1986. Specifically, DNAs from cow, chicken, pig, mouse and rat were digested with the restriction enzymes EcoRI and HindIII (8 μg of DNA per enzyme). The digested DNAs were separated overnight on an 0.7% gel at 20 volts for 16 hours (14 cm gel), and the DNA transferred to Nylon membranes using standard Southern blot techniques. For example, the zoo blot filter was treated at 65° C. in 0.1×SSC, 0.5% SDS, and 0.2M Tris, pH 8.0, for 30 minutes and then blocked overnight at 42° C. in 5× SSC, 10% PEG 8000, 20 mM $NaPO_4$ pH 6.8, 100 μg/ml Salmon Sperm DNA, 1× Denhardt's, 50% formamide, 0.1% SDS, and 2 μg/ml C_ot-1 DNA.

The cosmid and P1 clones to be analyzed were digested with a restriction enzyme to release the human DNA from the vector DNA. The DNA was separated on a 14 cm, 0.5% agarose gel run overnight at 20 volts for 16 hours. The human DNA bands were cut out of the gel and electroeluted from the gel wedge at 100 volts for at least two hours in 0.5× Tris Acetate buffer (Maniatis et al., 1982). The eluted Not I digested DNA (~15 kb to 25 kb) was then digested with EcoRI restriction enzyme to give smaller fragments (~0.5 kb to 5.0 kb) which melt apart more easily for the next step of labeling the DNA with radionucleotides. The DNA fragments were labeled by means of the hexamer random prime labeling method (Boehringer-Mannheim, Cat. #1004760). The labeled DNA was spermine precipitated (add 100 μl TE, 5 μl 0.1M spermine, and 5 μl of 10 mg/ml salmon sperm DNA) to remove unincorporated radionucleotides. The labeled DNA was then resuspended in 100 μl TE, 0.5M NaCl at 65° C. for 5 minutes and then blocked with Human C_ot-1 DNA for 2–4 hrs. as per the manufacturer's instructions (Gibco/BRL, Cat. #5279SA). The C_ot-1 blocked probe was incubated on the zoo blot filters in the blocking solution overnight at 42° C. The filters were washed for 30 minutes at room temperature in 2×SSC, 0.1% SDS, and then in the same buffer for 30 minutes at 55° C. The filters were then exposed 1 to 3 days at −70° C. to Kodak XAR-5 film with an intensifying screen. Thus, the zoo blots were hybridized with either the pool of Eco-R1 fragments from the insert, or each of the fragments individually.

HTF island analysis. The second method for identifying cosmids to use as probes on the cDNA libraries was HTF island analysis. Since the pulsed-field map can reveal HTF islands, cosmids that map to these HTF island regions were analyzed with priority. HTF islands are segments of DNA which contain a very high frequency of unmethylated CpG dinucleotides (Tonolio et al., 1990) and are revealed by the clustering of restriction sites of enzymes whose recognition sequences include CpG dinucleotides. Enzymes known to be useful in HTF-island analysis are AscI, NotI, BssHII, EagI, SacII, NaeI, NarI, SmaI, and MluI (Anand, 1992). A pulsed-field map was created using the enzymes NotI, NruI, EagI, SacII, and SalI, and two HTF islands were found. These islands are located in the distal end of the region, one being distal to the GP2B locus, and the other being proximal to the same locus, both outside the BRCA1 region. The cosmids derived from the YACs that cover these two locations were analyzed to identify those that contain these restriction sites, and thus the HTF islands.

cDNA screening. Those clones that contain HTF islands or show hybridization to other species DNA besides human are likely to contain coding sequences. The human DNA from these clones was isolated as whole insert or as EcoR1 fragments and labeled as described above. The labeled DNA was used to screen filters of various cDNA libraries under the same conditions as the zoo blots except that the cDNA filters undergo a more stringent wash of 0.1×SSC, 0.1% SDS at 65° C. for 30 minutes twice.

Most of the cDNA libraries used to date in our studies (libraries from normal breast tissue, breast tissue from a woman in her eighth month of pregnancy and a breast malignancy) were prepared at Clonetech, Inc. The cDNA library generated from breast tissue of an 8 month pregnant woman is available from Clonetech (Cat. #HL1037a) in the Lambda gt-10 vector, and is grown in C600Hfl bacterial host cells. Normal breast tissue and malignant breast tissue samples were isolated from a 37 year old Caucasian female and one-gram of each tissue was sent to Clonetech for mRNA processing and cDNA library construction. The latter two libraries were generated using both random and oligo-dT priming, with size selection of the final products which were then cloned into the Lambda Zap II vector, and grown in XL1-blue strain of bacteria as described by the manufacturer. Additional tissue-specific cDNA libraries include human fetal brain (Stratagene, Cat. 936206), human testis (Clonetech Cat. HL3024), human thymus (Clonetech Cat. HL1127a), human brain (Clonetech Cat. HL11810), human placenta (Clonetech Cat 1075b), and human skeletal muscle (Clonetech Cat. HL1124b).

The cDNA libraries were plated with their host cells on NZCYM plates, and filter lifts are made in duplicate from each plate as per Maniatis et al. (1982). Insert (human) DNA from the candidate genomic clones was purified and radioactively labeled to high specific activity. The radioactive DNA was then hybridized to the cDNA filters to identify those cDNAs which correspond to genes located within the candidate cosmid clone. cDNAs identified by this method were picked, replated, and screened again with the labeled clone insert or its derived EcoR1 fragment DNA to verify their positive status. Clones that were positive after this second round of screening were then grown up and their DNA pitied for Southern blot analysis and sequencing. Clones were either purified as plasmid through in vivo excision of the plasmid from the Lambda vector as described in the protocols from the manufacturers, or isolated from the Lambda vector as a restriction fragment and subcloned into plasmid vector.

The Southern blot analysis was performed in duplicate, one using the original genomic insert DNA as a probe to verify that cDNA insert contains hybridizing sequences. The second blot was hybridized with cDNA insert DNA from the largest cDNA clone to identify which clones represent the same gene. All cDNAs which hybridize with the genomic clone and are unique were sequenced and the DNA analyzed to determine if the sequences represent known or unique genes. All cDNA clones which appear to be unique were further analyzed as candidate BRCA1 loci. Specifically, the clones are hybridized to Northern blots to look for breast specific expression and differential expression in normal versus breast tumor RNAs. They are also analyzed by PCR on clones in the BRCA1 region to verify their location. To map the extent of the locus, full length cDNAs are isolated and their sequences used as PCR probes on the YACs and the clones surrounding and including the original identifying clones. Intron-exon boundaries are then further defined through sequence analysis.

We have screened the normal breast, 8 month pregnant breast and fetal brain cDNA libraries with zoo blot-positive Eco R1 fragments from cosmid BAC and P1 clones in the region. Potential BRCA1 cDNA clones were identified among the three libraries. Clones were picked, replated, and screened again with the original probe to verify that they were positive.

Analysis of hybrid-selected cDNA. cDNA fragments obtained from direct selection were checked by Southern blot hybridization against the probe DNA to verify that they originated from the contig. Those that passed this test were sequenced in their entirety. The set of DNA sequences obtained in this way were then checked against each other to find independent clones that overlapped. For example, the clones 694-65, 1240-1 and 1240-33 were obtained independently and subsequently shown to derive from the same contiguous cDNA sequence which has been named EST:489:1.

Analysis of candidate clones. One or more of the candidate genes generated from above were sequenced and the information used for identification and classification of each expressed gene. The DNA sequences were compared to known genes by nucleotide sequence comparisons and by translation in all frames followed by a comparison with known amino acid sequences. This was accomplished using Genetic Data Environment (GDE) version 2.2 software and the Basic Local Alignment Search Tool (Blast) series of client/server software packages (e.g., BLASTN 1.3.13MP), for sequence comparison against both local and remote sequence databases (e.g., GenBank), running on Sun SPARC workstations. Sequences reconstructed from collections of cDNA clones identified with the cosmids and P1s have been generated. All candidate genes that represented new sequences were analyzed further to test their candidacy for the putative BRCA1 locus.

Mutation screening. To screen for mutations in the affected pedigrees, two different approaches were followed. First, genomic DNA isolated from family members known to carry the susceptibility allele of BRCA1 was used as a template for amplification of candidate gene sequences by PCR. If the PCR primers flank or overlap an intron/exon boundary, the amplified fragment will be larger than predicted from the cDNA sequence or will not be present in the amplified mixture. By a combination of such amplification experiments and sequencing of P1, BAC or cosmid clones using the set of designed primers it is possible to establish the intron/exon structure and ultimately obtain the DNA sequences of genomic DNA from the pedigrees.

A second approach that is much more rapid if the intron/exon structure of the candidate gene is complex involves sequencing fragments amplified from pedigree lymphocyte cDNA. cDNA synthesized from lymphocyte mRNA extracted from pedigree blood was used as a substrate for PCR amplification using the set of designed primers. If the candidate gene is expressed to a significant extent in lymphocytes, such experiments usually produce amplified fragments that can be sequenced directly without knowledge of intron/exon junctions.

The products of such sequencing reactions were analyzed by gel electrophoresis to determine positions in the sequence that contain either mutations such as deletions or insertions, or base pair substitutions that cause amino acid changes or other detrimental effects.

Any sequence within the BRCA1 region that is expressed in breast is considered to be a candidate gene for BRCA1. Compelling evidence that a given candidate gene corresponds to BRCA1 comes from a demonstration that pedigree families contain defective alleles of the candidate.

EXAMPLE 8

Identification of BRCA1

Identification of BRCA1. Using several strategies, a derailed map of transcripts was developed for the 600 kb region of 17q21 between D17S1321 and D17S1324. Candidate expressed sequences were defined as DNA sequences obtained from: 1) direct screening of breast, fetal brain, or lymphocyte cDNA libraries, 2) hybrid selection of breast, lymphocyte or ovary cDNAs, or 3) random sequencing of genomic DNA and prediction of coding exons by XPOUND (Thomas and Skolnick, 1994). These expressed sequences in many cases were assembled into contigs composed of several independently identified sequences. Candidate genes may comprise more than one of these candidate expressed sequences. Sixty-five candidate expressed sequences within this region were identified by hybrid selection, by direct screening of cDNA libraries, and by random sequencing of P1 subclones. Expressed sequences were characterized by transcript size, DNA sequence, database comparison, expression pattern, genomic structure, and, most importantly, DNA sequence analysis in individuals from kindreds segregating 17q-linked breast and ovarian cancer susceptibility.

Three independent contigs of expressed sequence, 1141:1 (649 bp), 694:5 (213 bp) and 754:2 (1079 bp) were isolated and eventually shown to represent portions of BRCA1. When ESTs for these contigs were used as hybridization probes for Northern analysis, a single transcript of approximately 7.8 kb was observed in normal breast mRNA, suggesting that they encode different portions of a single gene. Screens of breast, fetal brain, thymus, testes, lymphocyte and placental cDNA libraries and PCR experiments with breast mRNA linked the 1141:1, 694:5 and 754:2 contigs. 5' RACE experiments with thymus, testes, and breast mRNA extended the contig to the putative 5' end, yielding a composite full length sequence. PCR and direct sequencing of P1 s and BACs in the region were used to identify the location of introns and allowed the determination of splice donor and acceptor sites. These three expressed sequences were merged into a single transcription unit that proved in the final analysis to be BRCA1. This transcription unit is located adjacent to D17S855 in the center of the 600 kb region (FIG. 4).

Combination of sequences obtained from cDNA clones, hybrid selection sequences, and amplified PCR products allowed construction of a composite full length BRCA1 cDNA (SEQ ID NO:1). The sequence of the BRCA1 cDNA (up through the stop codon) has also been deposited with GenBank and assigned accession number U-14680. This deposited sequence is incorporated herein by reference. The cDNA clone extending farthest in the 3' direction contains a poly(A) tract preceded by a polyadenylation signal. Conceptual translation of the cDNA revealed a single long open reading frame of 208 kilodaltons (amino acid sequence: SEQ ID NO:2) with a potential initiation codon flanked by sequences resembling the Kozak consensus sequence (Kozak, 1987). Smith-Waterman (Smith and Waterman, 1981) and BLAST (Altschul et al., 1990) searches identified a sequence near the amino terminus with considerable homology to zinc-finger domains (FIG. 5). This sequence contains cysteine and histidine residues present in the consensus C3HC4 zinc-finger motif and shares multiple other residues with zinc-finger proteins in the databases. The BRCA1 gene is composed of 23 coding exons arrayed over more than 100 kb of genomic DNA (FIG. 6). Northern blots using fragments of the BRCA1 cDNA as probes identified a single transcript of about 7.8 kb, present most abundantly in breast, thymus and testis, and also present in ovary (FIG. 7). Four alternatively spliced products were observed as independent cDNA clones; 3 of these were detected in breast and 2 in ovary mRNA (FIG. 6). A PCR survey from tissue cDNAs further supports the idea that there is considerable heterogeneity near the 5' end of transcripts from this gene; the molecular basis for the heterogeneity involves differential choice of the first splice donor site, and the changes detected all alter the transcript in the region 5' of the identified start codon. We have detected six potential alternate splice donors in this 5' untranslated region, with the longest deletion being 1,155 bp. The predominant form of the BRCA1 protein in breast and ovary lacks exon 4. The nucleotide sequence for BRCA1 exon 4 is shown in SEQ ID NO:11, with the predicted amino acid sequence shown in SEQ ID NO:12.

Additional 5' sequence of BRCA1 genomic DNA is set forth in SEQ ID NO:13. The G at position 1 represents the potential start site in testis. The A in position 140 represents the potential start site in somatic tissue. There are six alternative splice forms of this 5' sequence as shown in FIG. 8. The G at position 356 represents the canonical first splice donor site. The G at position 444 represents the first splice donor site in two clones (testis 1 and testis 2). The G at position 889 represents the first splice donor site in thymus 3. A fourth splice donor site is the G at position 1230. The T at position 1513 represents the splice acceptor site for all of the above splice donors. A fifth alternate splice form has a first splice donor site at position 349 with a first acceptor site at position 591 and a second splice donor site at position 889 and a second acceptor site at position 1513. A sixth alternate form is unspliced in this 5' region. The A at position 1532 is the canonical start site, which appears at position 120 of SEQ ID NO:1. Partial genomic DNA sequences determined for BRCA1 are set forth in FIGS. 10A–10H and SEQ ID Numbers:14–34. The lower case letters (in FIGS. 10A–10H) denote intron sequence while the upper case letters denote exon sequence. Indefinite intervals within introns are designated with vvvvvvvvvvvvv in FIGS. 10A–10H. The intron/exon junctions are shown in Table 9. The CAG found at the 5' end of exons 8 and 14 is found in some cDNAs but not in others. Known polymorphic sites are shown in FIGS. 10A–10H in boldface type and are underlined. The known polymorphisms are listed in Tables 18 and 19.

Low stringency blots in which genomic DNA from organisms of diverse phylogenetic background were probed with BRCA1 sequences that lack the zinc-finger region revealed strongly hybridizing fragments in human, monkey, sheep and pig, and very weak hybridization signals in rodents. This result indicates that, apart from the zinc-finger domain, BRCA1 is conserved only at a moderate level through evolution.

Germline BRCA1 mutations in 17q-linked kindreds. The most rigorous test for BRCA1 candidate genes is to search for potentially disruptive mutations in carrier individuals from kindreds that segregate 17q-linked susceptibility to breast and ovarian cancer. Such individuals must contain BRCA1 alleles that differ from the wildtype sequence. The set of DNA samples used in this analysis consisted of DNA from individuals representing 8 different BRCA1 kindreds (Table 10).

TABLE 9

Exon	Base position*			Intron Borders	
No.	5'	3'	Length	5'	3'
e1	1	100	100	GATAAATTAAAACTGCGACTGCGCGGCGTG[35]**	GTAGTAGAGTCCCGGGAAAGGGACAGGGGG[36]
e2	101	199	99	ATATATATATGTTTTTCTAATGTGTTAAAG[37]	GTAAGTCAGCACAAGAGTGTATTAATTTGG[38]
e3	200	253	54	TTTCTTTTTCTCCCCCCCCTACCCTGCTAG[39]	GTAAGTTTGAATGTGTTATGTGGCTCCATT[40]
e4	***	***	111	AGCTACTTTTTTTTTTTTTTTTTGAGACAG[41]	GTAAGTGCACACCACCATATCCAGCTAAAT[42]
e5	254	331	78	AATTGTTCTTTCTTTCTTTATAATTTATAG[43]	GTATATAATTTGGTAATGATGCTAGGTTGG[44]
e6	332	420	89	GAGTGTGTTTCTCAAACAATTTAATTTCAG[45]	GTAAGTGTTGAATATCCCAAGAATGACACT[46]
e7	421	560	140	AAACATAATGTTTTCCCTTGTATTTTACAG[47]	GTAAAACCATTTGTTTTCTTCTTCTTCTTC[48]
e8	561	666	106	TGCTTGACTGTTCTTTACCATACTGTTTAG[49]	GTAAGGGTCTCAGGTTTTTTAAGTATTTAA[50]
e9	667	712	46	TGATTTATTTTTTGGGGGGAAATTTTTTAG[51]	GTGAGTCAAAGAGAACCTTTGTCTATGAAG[52]
e10	713	789	77	TCTTATTAGGACTCTGTCTTTTCCCTATAG[53]	GTAATGGCAAAGTTTGCCAACTTAACAGGC[54]
e11	790	4215	3426	GAGTACCTTGTTATTTTTGTATATTTTCAG[55]	GTATTGGAACCAGGTTTTTGTGTTTGCCCC[56]
e12	4216	4302	87	ACATCTGAACCTCTGTTTTTGTTATTTAAG[57]	AGGTAAAAAGCGTGTGTGTGTGTGCACATG[58]
e13	4303	4476	174	CATTTTCTTGGTACCATTTATCGTTTTTGA[59]	GTGTGTATTGTTGGCCAAACACTGATATCT[60]
e14	4477	4603	127	AGTAGATTTGTTTTCTCATTCCATTTAAAG[61]	GTAAGAAACATCAATGTAAAGATGCTGTGG[62]
e15	4604	4794	191	ATGGTTTTCTCCTTCCATTTATCTTTCTAG[63]**	GTAATATTCATCTGCTGTATTGGAACAAAC[64]
e16	4795	5105	311	TGTAAATTAAACTTCTCCCATTCCTTTCAG[65]	GTGAGTGTATCCATATGTATCTCCCTAATG[66]
e17	5106	5193	88	ATGATAATGGAATATTTGATTTAATTTCAG[67]	GTATACCAAGAACCTTTACAGAATACCTTG[68]
e18	5194	5271	78	CTAATCCTTTGAGTGTTTTTCATTCTGCAG[69]	GTAAGTATAATACTATTTCTCCCCTCCTCC[70]
e19	5272	5312	41	TGTAACCTGTCTTTTCTATGATCTCTTTAG[71]	GTAAGTACTTGATGTTACAAACTAACCAGA[72]
e20	5313	5396	84	TCCTGATGGGTTGTGTTTGGTTTCTTTCAG[73]	GTAAAGCTCCCTCCCTCAAGTTGACAAAAA[74]
e21	5397	5451	55	CTGTCCCTCTCTCTTCCTCTCTTCTTCCAG[75]	GTAAGAGCCTGGGAGAACCCCAGAGTTCCA[76]
e22	5452	5525	74	AGTGATTTTACATGTAAATGTCCATTTTAG[77]	GTAAGTATTGGGTGCCCTGTCAGTGTGGGA[78]
e23	5526	5586	61	TTGAATGCTCTTTCCTTCCTGGGGATCCAG[79]	GTAAGGTGCCTCGCATGTACCTGTGCTATT[80]
e24	5587	5914	328	CTAATCTCTGCTTGTGTTCTCTGTCTCCAG[81]	

*Base numbers in SEQ ID NO:1.

**Numbers in superscript refer to SEQ ID NOS.

***e4 from SEQ ID NO:11.

TABLE 10

KINDRED DESCRIPTIONS AND ASSOCIATED LOD SCORES

	Cases (n)			Sporadic	LOD	
Kindred	Br	Br < 50	Ov	Cases[1] (n)	Score	Marker(s)
2082	31	20	22	7	9.49	D17S1327
2099	22	14	2*	0	2.36	D17S800/D17S855[2]
2035	10	8	1*	0	2.25	D17S1327
1901	10	7	1*	0	1.50	D17S855
1925	4	3	0	0	0.55	D17S579
1910	5	4	0	0	0.36	D17S579/D17S250[2]
1927	5	4	0	1	−0.44	D17S250
1911	8	5	0	2	−0.20	D17S250

[1] Number of women with breast cancer (diagnosed under age 50) or ovarian cancer (diagnosed at any age) who do not share the BRCA1-linked haplotype segregating in the remainder of the cases in the kindred.

[2] Multipoint LOD score calculated using both markers

*Kindred contains one individual who had both breast and ovarian cancer; this individual is counted as a breast cancer case and as an ovarian cancer case.

The logarithm of the odds (LOD) scores in these kindreds range from 9.49 to −0.44 for a set of markers in 17q21. Four of the families have convincing LOD scores for linkage, and 4 have low positive or negative LOD scores. The latter kindreds were included because they demonstrate haplotype sharing at chromosome 17q21 for at least 3 affected members. Furthermore, all kindreds in the set display early age of breast cancer onset and 4 of the kindreds include at least one case of ovarian cancer, both hallmarks of BRCA1 kindreds. One kindred, 2082, has nearly equal incidence of breast and ovarian cancer, an unusual occurrence given the relative rarity of ovarian cancer in the population. All of the kindreds except two were ascertained in Utah. K2035 is from the midwest. K2099 is an African-American kindred from the southern USA.

In the initial screen for predisposing mutations in BRCA1, DNA from one individual who carries the predisposing haplotype in each kindred was tested. The 23 coding exons and associated splice junctions were amplified either from genomic DNA samples or from cDNA prepared from lymphocyte mRNA. When the amplified DNA sequences were compared to the wildtype sequence, 4 of the 8 kindred samples were found to contain sequence variants (Table 11).

TABLE 11

PREDISPOSING MUTATIONS

Kindred Number	Mutation	Coding Effect	Location*
2082	C→T	Gln→Stop	4056
1910	extra C	frameshift	5385
2099	T→G	Met→Arg	5443
2035	?	loss of transcript	
1901	11 bp deletion	frameshift	189

*In Sequence ID NO: 1

All four sequence variants are heterozygous and each appears in only one of the kindreds. Kindred 2082 contains a nonsense mutation in coding exon 10 (FIG. 9A), Kindred 1910 contains a single nucleotide insertion in coding exon 19 (FIG. 9B), and Kindred 2099 contains a missense mutation in coding exon 20, resulting in a Met→Arg substitution (FIG. 9C). The frameshift and nonsense mutations are likely disruptive to the function of the BRCA1 product. The peptide encoded by the frameshift allele in Kindred 1910 would contain an altered amino acid sequence beginning 107 residues from the wildtype C-terminus. The peptide encoded by the frameshift allele in Kindred 1901 would contain an altered amino acid sequence beginning with the 24th residue from the wildtype N-terminus. The mutant allele in Kindred 2082 would encode a protein missing 548 residues from the C-terminus. The missense substitution observed in Kindred 2099 is potentially disruptive as it causes the replacement of a small hydrophobic amino acid (Met), by a large charged residue (Arg). Eleven common polymorphisms were also identified, 8 in coding sequence and 3 in introns.

The individual studied in Kindred 2035 evidently contains a regulatory mutation in BRCA1. In her cDNA, a polymorphic site (A→G at base 3667) appeared homozygous, whereas her genomic DNA revealed heterozygosity at this position (FIG. 9C). A possible explanation for this observation is that mRNA from her mutated BRCA1 allele is absent due to a mutation that affects its production or stability. This possibility was explored further by examining 5 polymorphic sites in the BRCA1 coding region, which are separated by as much as 3.5 kb in the BRCA1 transcript. In all cases where her genomic DNA appeared heterozygous for a polymorphism, cDNA appeared homozygous. In individuals from other kindreds and in non-haplotype carriers in Kindred 2035, these polymorphic sites could be observed as heterozygous in cDNA, implying that amplification from cDNA was not biased in favor of one allele. This analysis indicates that a BRCA1 mutation in Kindred 2035 either prevents transcription or causes instability or aberrant splicing of the BRCA1 transcript.

Cosegregation of BRCA1 mutations with BRCA1 haplotypes and population frequency analysis.

In addition to potentially disrupting protein function, two criteria must be met for a sequence variant to qualify as a candidate predisposing mutation. The variant must: 1) be present in individuals from the kindred who carry the predisposing BRCA1 haplotype and absent in other members of the kindred, and 2) be rare in the general population.

Each mutation was tested for cosegregation with BRCA1. For the frameshift mutation in Kindred 1910, two other haplotype carriers and one non-carrier were sequenced (FIG. 9B). Only the carriers exhibited the frameshift mutation. The C to T change in Kindred 2082 created a new AvrII restriction site. Other carriers and non-carriers in the kindred were tested for the presence of the restriction site (FIG. 9A). An allele-specific oligonucleotide (ASO) was designed to detect the presence of the sequence variant in Kindred 2099. Several individuals from the kindred, some known to carry the haplotype associated with the predisposing allele, and others known not to carry the associated haplotype, were screened by ASO for the mutation previously detected in the kindred. In each kindred, the corresponding mutant allele was detected in individuals carrying the BRCA1-associated haplotype, and was not detected in noncarriers. In the case of the potential regulatory mutation observed in the individual from Kindred 2035, cDNA and genomic DNA from carriers in the kindred were compared for heterozygosity at polymorphic sites. In every instance, the extinguished allele in the cDNA sample was shown to lie on the chromosome that carries the BRCA1 predisposing allele (FIG. 9C).

To exclude the possibility that the mutations were simply common polymorphisms in the population, ASOs for each mutation were used to screen a set of normal DNA samples. Gene frequency estimates in Caucasians were based on random samples from the Utah population. Gene frequency estimates in African-Americans were based on 39 samples provided by M. Peracek-Vance which originate from

African-Americans used in her linkage studies and 20 newborn Utah African-Americans. None of the 4 potential predisposing mutations was found in the appropriate control population, indicating that they are rare in the general population. Thus, two important requirements for BRCA1 susceptibility alleles were fulfilled by the candidate predisposing mutations: 1) cosegregation of the mutant allele with disease, and 2) absence of the mutant allele in controls, indicating a low gene frequency in the general population.

Phenotypic Expression of BRCA1 Mutations. The effect of the mutations on the BRCA1 protein correlated with differences in the observed phenotypic expression in the BRCA1 kindreds. Most BRCA1 kindreds have a moderately increased ovarian cancer risk, and a smaller subset have high risks of ovarian cancer, comparable to those for breast cancer (Easton et al., 1993). Three of the four kindreds in which BRCA1 mutations were detected fall into the former category, while the fourth (K2082) falls into the high ovarian cancer risk group. Since the BRCA1 nonsense mutation found in K2082 lies closer to the amino terminus than the other mutations detected, it might be expected to have a different phenotype. In fact, Kindred K2082 mutation has a high incidence of ovarian cancer, and a later mean age at diagnosis of breast cancer cases than the other kindreds (Goldgar et al., 1994). This difference in age of onset could be due to an ascertainment bias in the smaller, more highly penetrant families, or it could reflect tissue-specific differences in the behavior of BRCA1 mutations. The other 3 kindreds that segregate known BRCA1 mutations have, on average, one ovarian cancer for every 10 cases of breast cancer, but have a high proportion of breast cancer cases diagnosed in their late 20's or early 30's. Kindred 1910, which has a frameshift mutation, is noteworthy because three of the four affected individuals had bilateral breast cancer, and in each case the second tumor was diagnosed within a year of the first occurrence. Kindred 2035, which segregates a potential regulatory BRCA1 mutation, might also be expected to have a dramatic phenotype. Eighty percent of breast cancer cases in this kindred occur under age 50. This figure is as high as any in the set, suggesting a BRCA1 mutant allele of high penetrance (Table 10).

Although the mutations described above clearly are deleterious, causing breast cancer in women at very young ages, each of the four kindreds with mutations includes at least one woman who carries the mutation who lived until age 80 without developing a malignancy. It will be of utmost importance in the studies that follow to identify other genetic or environmental factors that may ameliorate the effects of BRCA1 mutations.

In four of the eight putative BRCA1-linked kindreds, potential predisposing mutations were not found. Three of these four have LOD scores for BRCA1-linked markers of less than 0.55. Thus, these kindreds may not in reality segregate BRCA1 predisposing alleles. Alternatively, the mutations in these four kindreds may lie in regions of BRCA1 that, for example, affect the level of transcript and therefore have thus far escaped detection.

Role of BRCA1 in Cancer. Most tumor suppressor genes identified to date give rise to protein products that are absent, nonfunctional, or reduced in function. The majority of TP53 mutations are missense; some of these have been shown to produce abnormal p53 molecules that interfere with the function of the wildtype product (Shaulian et al. 1992; Srivastava et al., 1993). A similar dominant negative mechanism of action has been proposed for some adenomatous polyposis coli (APC) alleles that produce truncated molecules (Su et al., 1993), and for point mutations in the Wilms' tumor gene (WT1) that alter DNA binding of the protein (Little et al., 1993). The nature of the mutations observed in the BRCA1 coding sequence is consistent with production of either dominant negative proteins or nonfunctional proteins. The regulatory mutation inferred in Kindred 2035 cannot be a dominant negative; rather, this mutation likely causes reduction or complete loss of BRCA1 expression from the affected allele.

The BRCA1 protein contains a C_3HC_4 zinc-finger domain, similar to those found in numerous DNA binding proteins and implicated in zinc-dependent binding to nucleic acids. The first 180 amino acids of BRCA1 contain five more basic residues than acidic residues. In contrast, the remainder of the molecule is very acidic, with a net excess of 70 acidic residues. The excess negative charge is particularly concentrated near the C-terminus. Thus, one possibility is that BRCA1 encodes a transcription factor with an N-terminal DNA binding domain and a C-terminal transactivational "acidic blob" domain. Interestingly, another familial tumor suppressor gene, WT1, also contains a zinc-finger motif (Haber et al., 1990). Many cancer predisposing mutations in WT1 alter zinc-finger domains (Little et al., 1993; Haber et al., 1990; Little et al., 1992). WT1 encodes a transcription factor, and alternative splicing of exons that encode parts of the zinc-finger domain alter the DNA binding properties of WT1 (Bickmore et al., 1992). Some alternatively spliced forms of WT1 mRNA generate molecules that act as transcriptional repressors (Drummond et al., 1994). Some BRCA1 splicing variants may alter the zinc-finger motif, raising the possibility that a regulatory mechanism similar to that which occurs in WT1 may apply to BRCA1.

EXAMPLE 9

Analysis of Tumors for BRCA1 Mutations

To focus the analysis on tumors most likely to contain BRCA1 mutations, primary breast and ovarian carcinomas were typed for LOH in the BRCA1 region. Three highly polymorphic, simple tandem repeat markers were used to assess LOH: D17S1323 and D17S855, which are intragenic to BRCA1, and D17S1327, which lies approximately 100 kb distal to BRCA1. The combined LOH frequency in informative cases (i.e., where the germline was heterozygous) was 32/72 (44%) for the breast carcinomas and 12/21 (57%) for the ovarian carcinomas, consistent with previous measurements of LOH in the region (Futreal et al., 1992b; Jacobs et al., 1993; Sato et al., 1990; Eccles et al., 1990; Cropp et al., 1994). The analysis thus defined a panel of 32 breast tumors and 12 ovarian tumors of mixed race and age of onset to be examined for BRCA mutations. The complete 5,589 bp coding region and intron/exon boundary sequences of the gene were screened in this tumor set by direct sequencing alone or by a combination of single-strand conformation analysis (SSCA) and direct sequencing.

A total of six mutations was found, one in an ovarian tumor, four in breast tumors and one in a male unaffected haplotype carrier (Table 12). One mutation, Glu1541Ter, introduced a stop codon that would create a truncated protein missing 273 amino acids at the carboxy terminus. In addition, two missense mutations were identified. These are Ala1708Glu and Met1775Arg and involve substitutions of small, hydrophobic residues by charged residues. Patients 17764 and 19964 are from the same family. In patient OV24 nucleotide 2575 is deleted and in patients 17764 and 19964 nucleotides 2993–2996 are deleted.

TABLE 12

Patient	Codon	Predisposing Mutations Nucleotide Change	Amino Acid Change	Age of Onset	Family History
BT098	1541	GAG→TAG	Glu→Stop	39	−
OV24	819	1 bp deletion	frameshift	44	
BT106	1708	GCG→GAG	Ala→Glu	24	+
MC44	1775	ATG→AGG	Met→Arg	42	+
17764	958	4 bp deletion	frameshift	31	+
19964	958	4 bp deletion	frameshift		+*

*Unaffected haplotype carrier, male

Several lines of evidence suggest that all five mutations represent BRCA1 susceptibility alleles:

(i) all mutations are present in the germline;

(ii) all are absent in appropriate control populations, suggesting they are not common polymorphisms;

(iii) each mutant allele is retained in the tumor, as is the case in tumors from patients belonging to kindreds that segregate BRCA1 susceptibility alleles (Smith et al., 1992; Kelsell et al. 1993) (if the mutations represented neutral polymorphisms, they should be retained in only 50% of the cases);

(iv) the age of onset in the four breast cancer cases with mutations varied between 24 and 42 years of age, consistent with the early age of onset of breast cancer in individuals with BRCA1 susceptibility; similarly, the ovarian cancer case was diagnosed at 44, an age that falls in the youngest of all ovarian cancer cases; and finally,

(v) three of the five cases have positive family histories of breast or ovarian cancer found retrospectively in their medical records, although the tumor set was not selected with regard to this criterion.

BT106 was diagnosed at a very early age with breast cancer. Her mother had ovarian cancer, her father had melanoma, and her paternal grandmother also had breast cancer. Patient MC44, an African-American, had bilateral breast cancer at a very early age. This patient had a sister who died of breast cancer at a very early age. Her mutation (Met1775Arg) had been detected previously in Kindred 2099, an African-American family that segregates a BRCA1 susceptibility allele, and was absent in African-American and Caucasian controls. Patient MC44, to our knowledge, is unrelated to Kindred 2099. The detection of a rare mutant allele, once in a BRCA1 kindred and once in the germline of an apparently unrelated early-onset breast cancer case, suggests that the Met1775Arg change may be a common predisposing mutation in African-Americans. Collectively, these observations indicate that all four BRCA1 mutations in tumors represent susceptibility alleles; no somatic mutations were detected in the samples analyzed.

The paucity of somatic BRCA1 mutations is unexpected, given the frequency of LOH on 17q, and the usual role of susceptibility genes as tumor suppressors in cancer progression. There are three possible explanations for this result: (i) some BRCA1 mutations in coding sequences were missed by our screening procedure; (ii) BRCA1 somatic mutations fall primarily outside the coding exons; and (iii) LOH events in 17q do not reflect BRCA1 somatic mutations.

If somatic BRCA1 mutations truly are rare in breast and ovary carcinomas, this would have strong implications for the biology of BRCA1. The apparent lack of somatic BRCA1 mutations implies that there may be some identical difference in the genesis of tumors in genetically predisposed BRCA1 carriers, compared with tumors in the general population. For example, mutations in BRCA1 may have an effect only on minor formation at a specific stage early in breast and ovarian development. This possibility is consistent with a primary function for BRCA1 in premenopausal breast cancer. Such a model for the role of BRCA1 in breast and ovarian cancer predicts an interaction between reproductive hormones and BRCA1 function. However, no clinical or pathological differences in familial versus sporadic breast and ovary tumors, other than age of onset, have been described (Lynch et al., 1990). On the other hand, the recent finding of increased TP53 mutation and microsatellite instability in breast tumors from patients with a family history of breast cancer (Glebov et al., 1994) may reflect some difference in tumors that arise in genetically predisposed persons. The involvement of BRCA1 in this phenomenon can now be addressed directly. Alternatively, the lack of somatic BRCA1 mutations may result from the existence of multiple genes that function in the same pathway of tumor suppression as BRCA1, but which collectively represent a more favored target for mutation in sporadic tumors. Since mutation of a single element in a genetic pathway is generally sufficient to disrupt the pathway, BRCA1 might mutate at a rate that is far lower than the sum of the mutational rates of the other elements.

A separate study to analyze tumors for BRCA1 mutations was performed in Japan. A panel of 103 patients representing early-onset cases (<35 years of age) (46 patients), members of multiply-affected families (12 patients), and/or had developed bilateral breast cancers (59 patients) were screened for mutations in BRCA1. Primary breast tumors from these patients were screened for mutations in coding exons of BRCA1 using single-strand conformation polymorphism (SSCP) analysis. For exon 11, which is 3425 bp long, PCR primers were designed to amplify eleven overlapping segments of this exon separately. Each of the other 22 exons was amplified individually in a single PCR. Thus 33 PCR-SSCP analyses were carried out for each case. Mutations were detected in tumors from four patients, all of whom had developed breast cancers bilaterally (Table 12A). One mutation resulted in a frame shift due to a 2 bp deletion (deletion of AA) at codon 797. This gives rise to a truncated protein missing 1065 amino acids at the COOH terminus. A second mutation was a nonsense mutation at codon 1214 due to a G→T transversion of the first nucleotide of the codon. This results in a premature stop codon in place of glutamic acid at this site and results in a truncated protein missing 649 amino acids at the COOH terminus. There were also two missense mutations. One was a G→A transition at the first nucleotide of codon 271 resulting in a Val→Met substitution. The second was at codon 1150 (a C→T transition in the first nucleotide of the codon) causing a Pro→Ser substitution, a replacement of a hydrophobic nonpolar amino acid with a polar uncharged amino acid. These mutations were all found to be germline mutations. The mean age of onset in these four patients was 49. These studies also found a common neutral polymorphism of either C or T at the first nucleotide of codon 771.

TABLE 12A

Predisposing Mutations				
Patient	Codon	Nucleotide Change	Amino Acid Change	Age of Onset
23	1150	CCT→TCT	Pro→Ser	49 & 64
44	1214	GAG→TAG	Glu→Stop	51 & 51
98	271	GTG→ATG	Val→Met	45 & 45
100	797	2 bp deletion	frameshift	50 & 71
5	482-483	4 bp deletion	frameshift	45
6	856	TAT→CAT	Tyr→His	54
7	271	GTG→ATG	Val→Met	49 & 49
8	852	1 bp deletion	frameshift	62

Although patients 98 and 7 show the same mutation, they are not related to each other.

EXAMPLE 10

Analysis of the BRCA1 Gene

The structure and function of BRCA1 gene are determined according to the following methods.

Biological Studies. Mammalian expression vectors containing BRCA1 cDNA are constructed and transfected into appropriate breast carcinoma cells with lesions in the gene. Wild-type BRCA1 cDNA as well as altered BRCA1 cDNA are utilized. The altered BRCA1 cDNA can be obtained from altered BRCA1 alleles or produced as described below. Phenotypic reversion in cultures (e.g., cell morphology, doubling time, anchorage-independent growth) and in animals (e.g., tumorigenicity) is examined. The studies will employ both wild-type and mutant forms (Section B) of the gene.

Molecular Genetics Studies. In vitro mutagenesis is performed to construct deletion mutants and missense mutants (by single base-pair substitutions in individual codons and cluster charged→alanine scanning mutagenesis). The mutants are used in biological, biochemical and biophysical studies.

Mechanism Studies. The ability of BRCA1 protein to bind to known and unknown DNA sequences is examined. Its ability to transactivate promoters is analyzed by transient reporter expression systems in mammalian cells. Conventional procedures such as particle-capture and yeast two-hybrid system are used to discover and identify any functional partners. The nature and functions of the partners are characterized. These partners in turn are targets for drug discovery.

Structural Studies. Recombinant proteins are produced in *E. coli*, yeast, insect and/or mammalian cells and are used in crystallographical and NMR studies. Molecular modeling of the proteins is also employed. These studies facilitate structure-driven drug design.

EXAMPLE 11

Two Step Assay to Detect the Presence of BRAC1 in a Sample

Patient sample is processed according to the method disclosed by Antonarakis, et al. (1985), separated through a 1% agarose gel and transferred to nylon membrane for Southern blot analysis. Membranes are UV cross linked at 150 mJ using a GS Gene Linker (Bio-Rad). BRCA1 probe corresponding to nucleotide positions 3631-3930 of SEQ ID NO:1 is subcloned into pTZ18U. The phagemids are transformed into *E. coli* MV1190 infected with M13KO7 helper phage (Bio-Rad, Richmond, Calif.). Single stranded DNA is isolated according to standard procedures (see Sambrook, et al., 1989).

Blots are prehybridized for 15–30 min at 65° C. in 7% sodium dodecyl sulfate (SDS) in 0.5M $NaPO_4$. The methods follow those described by Nguyen, et al., 1992. The blots are hybridized overnight at 65° C. in 7% SDS, 0.5M $NaPO_4$ with 25–50 ng/ml single stranded probe DNA. Post-hybridization washes consist of two 30 min washes in 5% SDS, 40 mM $NaPO_4$ at 65° C., followed by two 30-min washes in 1% SDS, 40 mM $NaPO_4$ at 65° C.

Next the blots are rinsed with phosphate buffered saline (pH 6.8) for 5 min at room temperature and incubated with 0.2% casein in PBS for 30–60 min at room temperature and rinsed in PBS for 5 min. The blots are then preincubated for 5–10 minutes in a shaking water bath at 45° C. with hybridization buffer consisting of 6M urea, 0.3M NaCl, and 5× Denhardt's solution (see Sambrook, et al., 1989). The buffer is removed and replaced with 50–75 µl/cm^2 fresh hybridization buffer plus 2.5 nM of the covalently cross-linked oligonucleotide-alkaline phosphatase conjugate with the nucleotide sequence complementary to the universal primer site (UP-AP, Bio-Rad). The blots are hybridized for 20–30 min at 45° C. and post hybridization washes are incubated at 45° C. as two 10 min washes in 6M urea, 1× standard saline citrate (SSC), 0.1% SDS and one 10 min wash in 1×SSC, 0.1% Triton®X-100. The blots are rinsed for 10 min at room temperature with 1×SSC.

Blots are incubated for 10 min at room temperature with shaking in the substrate buffer consisting of 0.1M diethanolamine, 1 mM $MgCl_2$, 0.02% sodium azide, pH 10.0. Individual blots are placed in heat sealable bags with substrate buffer and 0.2 mM AMPPD (3-(2'-spiroadamantane)-4-methoxy-4-(3'-phosphoryloxy)phenyl-1,2-dioxetane, disodium salt, Bio-Rad). After a 20 min incubation at room temperature with shaking, the excess AMPPD solution is removed. The blot is exposed to X-ray film overnight. Positive bands indicate the presence of BRCA1.

EXAMPLE 12

Generation of Polyclonal Antibody against BRCA1

Segments of BRCA1 coding sequence were expressed as fusion protein in *E. coli*. The overexpressed protein was purified by gel elution and used to immunize rabbits and mice using a procedure similar to the one described by Harlow and Lane, 1988. This procedure has been shown to generate Abs against various other proteins (for example, see Kraemer, et al., 1993).

Briefly, a stretch of BRCA1 coding sequence was cloned as a fusion protein in plasmid PETSA (Novagen, Inc., Madison, Wis.). The BRCA1 incorporated sequence includes the amino acids corresponding to #1361–1554 of SEQ ID NO:2. After induction with IPTG, the overexpression of a fusion protein with the expected molecular weight was verified by SDS/PAGE. Fusion protein was purified from the gel by electroelution. The identification of the protein as the BRCA1 fusion product was verified by protein sequencing at the N-terminus. Next, the purified protein was used as immunogen in rabbits. Rabbits were immunized with 100 µg of the protein in complete Freund's adjuvant and boosted twice in 3 week intervals, first with 100 µg of immunogen in incomplete Freund's adjuvant followed by 100 µg of immunogen in PBS. Antibody containing serum is collected two weeks thereafter.

This procedure is repeated to generate antibodies against the mutant forms of the BRCA1 gene. These antibodies, in conjunction with antibodies to wild type BRCA1, are used to detect the presence and the relative level of the mutant forms in various tissues and biological fluids.

EXAMPLE 13

Generation of Monoclonal Antibodies Specific for BRCA1

Monoclonal antibodies are generated according to the following protocol. Mice are immunized with immunogen comprising intact BRCA1 or BRCA1 peptides (wild type or mutant) conjugated to keyhole limpet hemocyanin using glutaraldehyde or EDC as is well known.

The immunogen is mixed with an adjuvant. Each mouse receives four injections of 10 to 100 μg of immunogen and after the fourth injection blood samples are taken from the mice to determine if the serum contains antibody to the immunogen. Serum titer is determined by ELISA or RIA. Mice with sera indicating the presence of antibody to the immunogen are selected for hybridoma production.

Spleens are removed from immune mice and a single cell suspension is prepared (see Harlow and Lane, 1988). Cell fusions are performed essentially as described by Kohler and Milstein, 1975. Briefly, P3.65.3 myeloma cells (American Type Culture Collection, Rockville, Md.) are fused with immune spleen cells using polyethylene glycol as described by Harlow and Lane, 1988. Cells are plated at a density of 2×10^5 cells/well in 96 well tissue culture plates. Individual wells are examined for growth and the supernatants of wells with growth are tested for the presence of BRCA1 specific antibodies by ELISA or RIA using wild type or mutant BRCA1 target protein. Cells in positive wells are expanded and subcloned to establish and confirm monoclonality.

Clones with the desired specificities are expanded and grown as ascites in mice or in a hollow fiber system to produce sufficient quantities of antibody for characterization and assay development.

EXAMPLE 14

Sandwich Assay for BRCA1

Monoclonal antibody is attached to a solid surface such as a plate, tube, bead, or particle. Preferably, the antibody is attached to the well surface of a 96-well ELISA plate. 100 μl sample (e.g., serum, urine, tissue cytosol) containing the BRCA1 peptide/protein (wild-type or mutant) is added to the solid phase antibody. The sample is incubated for 2 hrs at room temperature. Next the sample fluid is decanted, and the solid phase is washed with buffer to remove unbound material. 100 μl of a second monoclonal antibody (to a different determinant on the BRCA1 peptide/protein) is added to the solid phase. This antibody is labeled with a detector molecule (e.g., 125-I, enzyme, fluorophore, or a chromophore) and the solid phase with the second antibody is incubated for two hrs at room temperature. The second antibody is decanted and the solid phase is washed with buffer to remove unbound material.

The mount of bound label, which is proportional to the amount of BRCA1 peptide/protein present in the sample, is quantitated. Separate assays are performed using monoclonal antibodies which are specific for the wild-type BRCA1 as well as monoclonal antibodies specific for each of the mutations identified in BRCA1.

EXAMPLE 15

Analysis of BRCA1 Mutations

The DNA samples which were screened for BRCA1 mutations were extracted from blood or tumor samples from patients with breast or ovarian cancer (or known carriers by haplotype analysis) who were participating in research studies on the genetics of breast cancer. All subjects signed appropriate informed consent. Table 13 details the number of samples, ascertainment criteria, and screening method for each set of samples screened.

TABLE 13

Sets of DNA Samples Screened for Mutations in BRCA1

Source of Samples	Description of Samples[1]	Screening Method[2]	No. Samples Screened	No. Mutations Found to Date
UTAH-2	Br/Ov Families	SEQ	10	2
MONTREAL	Br/Ov Families	SEQ	20	13
MSKCC-1	Br and Br/Ov Families	SEQ	14	2
NSK/UT-1	Early Onset Br Cases	SEQ	24	1
STRANG	Br and Br/Ov Families	SEQ	12	4
STOCKHOLM	Br and Br/Ov Families	SEQ	15	4
USC-1	Bilat Br Proband, High-Risk	SEQ	7	3
TUMOR-3	Early Onset Br Tumors	SEQ	14	1
USC-2	Bilat Br <50 + 1° rel Br	ASO	59	5
MSK/UT-2	Early Onset Br Cases	ASO	109	3
YN	Bilateral; Early Onset	SSCA	103	4
Texas	Br/Ov Families	SEQ	15	2
Utah	Br/Ov Families	SEQ	10	1
Fra	Br/Ov Families	SEQ	21	4
Tumorbank		SEQ		1
MSKCC-2	Early Onset Br Cases	SEQ	21	3

[1] Most sample groups contained a heterogeneous mixture of samples. The most representative description of each set is given.

[2] SEQ - Direct sequencing of PCR products; SSCA - Single Strand Conformation Assay; ASO - Allele-Specific Oligo

Although the original mutations described in Miki et al., 1994 were detected through screening of cDNA, 25 pairs of intronic PCR primers were used to amplify the complete coding sequence and splice junctions from genomic DNA for the majority of the remaining samples. Updated primer information is publicly available via anonymous ftp from morgan.med.utah.edu in the directory pub/BRCA1. Where possible, DNA sequence variations were tested for cosegregation with breast or ovarian cancer in the family. Further evidence of a causal role of a sequence variant in cancer was provided by proving the absence of the putative mutation in a set of control individuals. Screening for specific, previously-identified mutations in large sets of selected samples was performed using ASO hybridization.

Table 14 describes many of the mutations found screening the entire BRCA1 coding sequence as well as the intron/exon boundaries and by finding polymorphic sites in genomic DNA reduced to monomorphic sites in cDNA. Two common mutations were found and their frequencies in other samples were examined by ASO analysis (Table 15). Tables 16 and 17 describe the distribution of mutations by type and by location within the BRCA1 coding sequence, respectively. By far, the majority of mutations identified were frameshifts. Globally, no statistically significant departure from a random distribution across the coding sequence of BRCA1 was found (χ^2=2.00, 2 df, p=0.37) among the distinct mutations found in the coding sequence of BRCA1 to date.

TABLE 14

Mutations Identified by Complete Screening of the BRCA1 Gene

		# Cases			Mutation Description		
Sample Set	Family	BR	OV	Type[1]	Exon	Condon	Mutation[2]
TEXAS	132-000			FS	2	23	185 ins A → ter 40
MONTREAL	180	2	2	FS	2	23	185 del AG → ter 39
MONTREAL	235	4	2	FS	2	23	185 del AG → ter 39
MONTREAL	253	1	3	FS	2	23	185 del AG → ter 39
MONTREAL	255	0	7	FS	2	23	185 del AG → ter 39
MSKCC	210311	3	0	FS	2	23	185 del AG → ter 39
USC-1	008	2	1	FS	2	23	185 del AG → ter 39
PISA	27	8	5	MS	5	64	Cys 64 Arg
UTAH				SP	I-5	I-5	T → G ins 59 → ter 75
MSKCC	19921			SP	I-6	I-6	del A at −2 of 3' splice
TUMOR-3[4]	—	1	0	FS	11	270	926 ins 19 → ter 289
MSK/UT-1	—	1	0	FS	11	270	926 ins 10 → ter 289
YN98	—	1	0	MS	11	271	Val 271 Met
YN7	—	1	0	MS	11	271	Val 271 Met
MONTREAL	270	4	3	FS	11	339	1128 ins A → ter 345
STRANG	2903	1	2	FS	11	339	1128 ins A → ter 345
MONTREAL	185	1	3	FS	11	392	1294 del 40 → ter 396
PISA	6			FS	11	461	1499 ins A → ter 479
PISA	17			FS	11	461	1499 ins A → ter 479
PISA	31			FS	11	461	1499 ins A → ter 479
YN5	—	1	0	FS	11	482	del 4 → ter
USC-1	052	5	1	FS	11	655	2080 ins A → ter 672
USC-1	068	2	1	FS	11	655	2080 in sA → ter 672
PISA				MS	11	667	Gln 667 His
STRANG	2802	2	2	FS	11	725	2293 del G → ter 735
YN100	—	1	0	FS	11	797	2509 del AA → ter 799
TUMORimod	OV24	0	1	FS	11	819	2575 del C → ter 845
MONTREAL	179	2	3	MS	11	826	Thr 826 Lys
STOCKHOLM	AL48	3	1	FS	11	826	2596 del C → ter 845
STOCKHOLM	BR33	5	1	FS	11	826	2596 del C → ter 845
YN8		1	0	FS	11	852	del del 1 → ter 891
YN6		1	0	MS	11	856	Tyr 856 His
UTAH-2	2305	2	7	FS	11	958	2993 del 4 → ter 998
MONTREAL	218	5	1	FS	11	1002	3121 del A → ter 1023
MSK17572				MS	11	1008	Met 1008 Ile
STOCKHOLM	BR24	2	1	FS	11	1016	3166 ins 5 → ter 1025
MONTREAL				FS	11	1110	3447 del 4 → ter 1115
MONTREAL	448			FS	11	1110	3449 del 4 → ter 1115
TEXAS	BC110-001			FS	11	1111	3450 del 4 → ter 1115
YN23	—	1	0	MS	11	1150	Pro 1150 Ser
STOCKHOLM	PAL33	1	0	FS	11	1209	3745 del T → ter 1209
YN44	—	1	0	NS	11	1214	Glu 1214 ter
MSK12871				MS	11	1219	Glu 1219 Asp
TEXAS	BC215-000			FS	11	1252	3873 del 4 → ter 1262
UTAH-2	2039	3	2	MS	11	1347	Arg 1347 Gly
MONTREAL	183	4	1	FS	11	1355	4184 del 4 → ter 1364
STRANG	1900[3]	3	1	NS	13	1443	Arg 1443 ter
[illegible]		1	0	NS	15	1541	Gln 1541 ter
PISA	68			FS	16	1585	4873 del CA → ter 1620
[illegible]				MS	16	1628	Met 1628 Val
[illegible]	8622[5]	4	1	FS	16	1656	5085 del 19 → ter 1670
MONTREAL	101	2	2	FS	20	1756	5382 ins C → ter 1829
MONTREAL	162	3	1	FS	20	1756	5382 ins C → ter 1829
MONTREAL	166	5	2	FS	20	1756	5382 ins C → ter 1829

TABLE 14-continued

Mutations Identified by Complete Screening of the BRCA1 Gene

	# Cases		Mutation Description			
Sample Set	Family	BR	OV	Type[1]	Exon	Codon	Mutation[2]

Sample Set	Family	# Cases BR	# Cases OV	Type[1]	Exon	Codon	Mutation[2]
MONTREAL	279	4	0	FS	20	1756	5382 ins C → ter 1829
MSKCC	193549	0	3	FS	20	1756	5382 ins C → ter 1829
MSK7542				MS	24	1852	Thr 1852 Ser

[1] FS-Frameshift; NS-Nonsense; MS-Missense; SP-Splice Site.

[2] For Missense and Nonsense mutations, the mutation description contains wild type amino acid, affected codon, altered amino acid (or ter). For frameshift mutations, the format is: nucleotide, insertion or deletion, specific nucleotides changed (if <3) or number inserted or deleted (if >2) and the amino acid (accounting for the insertion or deletion) in which the frameshift results in a termination signal. Nucleotides refer to the BRCA1 cDNA sequence in GENBANK under Accession No. U-14680.

[3] The mutation in this family was independently identified in both the Myriad and University of Pennsylvania Labs.

[4] The mutation identified in this tumor was also found in the germline of the individual.

TABLE 15

Frequency of Two Common BRCA1 Mutations

Set	Number Studied	Number of Mutations Found 185 del AG	Number of Mutations Found 5382 ins C
USC-1	59	4	1
MSK/UT-2	109	3	0
GLASGOW-2	100	Not tested	3
GLASGOW-3	100	Not tested	2
CRC-OV	250	Not tested	1

TABLE 16

Observed Frequency of Different Types of Mutations

Mutation Type	Number (Percent) Distinct Mutations[1]	Number (Percent) All Mutations[2]
Frameshift	42 (65)	81 (72)
Nonsense	10 (16)	13 (12)
Missense	9 (14)	14 (12)
Other	3 (5)	5 (4)

[1] Identical mutations are counted only once in this column.

[2] Each sample in which a mutation has been identified is counted in this column.

TABLE 17

Distribution of Identified Mutations in BRCA1 Coding Sequence

Mutations	Amino Acids 1-621	Amino Acids 622-1242	Amino Acids 1243-1863
Distinct	18	23	21
All	44	28	39

Mutations have been found in many different regions of the gene-phenotypically severe mutations have been found both in the extreme 5' end of BRCA1 as well as in the extreme 3' portion of the gene. One such mutation found in a family with seven early-onset breast cancer cases produces a protein that is only missing the terminal 10 amino acids, indicating that this region of BRCA1 plays a role in normal gene function. It is noteworthy the overwhelming majority of alterations in BRCA1 have been either frameshift or nonsense mutations resulting in an unstable or truncated protein product.

In BRCA1, to date, two mutations appear to be relatively common. The 5382 ins C BRCA1 mutation in codon 1756 and the 185 del AG mutation in codon 23 were identified by direct sequencing in seven (10%) and eight (12%) of the 68 probands studied in the initial studies in which mutations were identified, respectively. In addition to these common mutations, additional mutations have been found in more than one family by a complete screen of the cDNA. Many of the probands screened to date for BRCA1 mutations were selected for having a high prior probability of having such mutations. Thus the mutations found in this set may not be representative of those which would be identified in other sets of patients. However, the two most frequent BRCA1 mutations (5382 ins C and 185 del AG) have been found multiple times in targeted screening in sets of probands who were either unselected for family history or ascertained with minimal family history.

Besides the mutations shown above, many polymorphisms were also detected during the screening of samples. These polymorphisms are listed in Tables 18 and 19.

Industrial Utility

As previously described above, the present invention provides materials and methods for use in testing BRCA1 alleles of an individual and an interpretation of the normal or predisposing nature of the alleles. Individuals at higher than normal risk might modify their lifestyles appropriately. In the case of BRCA1, the most significant non-genetic risk factor is the protective effect of an early, full term pregnancy. Therefore, women at risk could consider early childbearing or a therapy designed to simulate the hormonal effects of an early full-term pregnancy. Women at high risk would also strive for early detection and would be more highly motivated to learn and practice breast self examination. Such women would also be highly motivated to have regular mammograms, perhaps starting at an earlier age than the general population. Ovarian screening could also be undertaken at greater frequency. Diagnostic methods based on sequence analysis of the BRCA1 locus could also be applied to tumor detection and classification. Sequence analysis could be used to diagnose precursor lesions.

TABLE 18

Polymorphisms in BRCA1 Genomic DNA Exons

Name	Exon #	Codon	Base Position[1]	Base Change	Effect
PM01	11	356	1186	A ←→ G	gln ←→ arg
PM02	13	1436	4427	T ←→ C	ser ←→ ser
PM03	16	1613	4956	A ←→ G	ser ←→ gly
PM06	11	871	2731	C ←→ T	pro ←→ leu
PM07	11	1183	3667	A ←→ G	lys ←→ arg
PM09	11	694	2201	C ←→ T	ser ←→ ser
PM10	11	771	2430	T ←→ C	leu ←→ leu
PM12	16	1561	4801	C ←→ T	thr ←→ ile
PM14	11	1038	3233	A ←→ G	glu ←→ glu
PM17	9	197	730	C ←→ T	cys ←→ cys
PM18	11	693	2196	G ←→ A	asp ←→ asn
PM19	11	841	2640	C ←→ T	arg ←→ trp
PM20	11	1040	3238	G ←→ A	ser ←→ asn
PM21	4	612	48[3]	C ←→ T	ala ←→ val
PM22	11	327	1100	A ←→ G	thr ←→ thr
PM23	11	1316	4067	C ←→ A	phe ←→ leu
PM24	11	1008	3143	G ←→ A	met ←→ ile
PM25	11	1316	4067	C ←→ G	phe ←→ leu
PM26	11	1322	4083	A ←→ G	lys ←→ glu
PM27	11	1347	4158	A ←→ G	arg ←→ gly
PM28	11	707	2240	T ←→ C	gly ←→ gly
PM29	11	675	2144	A ←→ C	ala ←→ ala

[1] Base position as shown in SEQ ID NO:1

[2] Codon number with exon 4 included in the coding region

[3] Base position as shown in SEQ ID NO:11 (exon 4 alone)

TABLE 19

Polymorphisms in BRCA1 Genomic DNA Introns

Name	Intron #	Base Position[1]	Base Change	Effect
PM04	11	15284	C ←→ A	unknown
PM05	18	20334	A ←→ G	unknown
PM11	16	19231	G ←→ A	unknown
PM15	8	9106	del T	unknown
PM16	22	22914	T ←→ C	unknown
PMA02.1	1	1295	G ←→ A	unknown
PMA03.1	2	2141	G ←→ C	unknown
PMA06.1	5	3653	A ←→ G	unknown
PMA07.1	7	insert between 4391–4392	TTC	unknown
PMA08.1	7	6538	C ←→ T	unknown
PMA08.2	8	6823	A ←→ T	unknown
PMA09.2	9	9376	T ←→ C	unknown
PMA13.1	13	16243	G ←→ A	unknown
PMA15.1	14	insert between 17335–17336	CCAAC	unknown
PMA15.2	14	17399	A ←→ T	unknown
PMA15.3	14	17473	C ←→ G	unknown
PMA18.1	17	20138	C ←→ T	unknown
PMA22.1	21	22680	A ←→ G	unknown

[1] Base position as shown in FIGS. 10-H

With the evolution of the method and the accumulation of information about BRCA1 and other causative loci, it could become possible to separate cancers into benign and malignant.

Women with breast cancers may follow different surgical procedures if they are predisposed, and therefore likely to have additional cancers, than if they are not predisposed. Other therapies may be developed, using either peptides or small molecules (rational drug design). Peptides could be the missing gene product itself or a portion of the missing gene product. Alternatively, the therapeutic agent could be another molecule that mimics the deleterious gene's function, either a peptide or a nonpeptidic molecule that seeks to counteract the deleterious effect of the inherited locus. The therapy could also be gene based, through introduction of a normal BRCA1 allele into individuals to make a protein which will counteract the effect of the deleterious allele. These gene therapies may take many forms and may be directed either toward preventing the tumor from forming, curing a cancer once it has occurred, or stopping a cancer from metastasizing.

It will be appreciated that the methods and compositions of the instant invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent to the artisan that other embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

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LIST OF PATENTS AND PATENT APPLICATIONS

U.S. Pat. No. 3,817,837
U.S. Pat. No. 3,850,752
U.S. Pat. No. 3,939,350
U.S. Pat. No. 3,996,345
U.S. Pat. No. 4,275,149
U.S. Pat. No. 4,277,437
U.S. Pat. No. 4,366,241
U.S. Pat. No. 4,376,110
U.S. Pat. No. 4,486,530
U.S. Pat. No. 4,683,195
U.S. Pat. No. 4,683,202
U.S. Pat. No. 4,816,567
U.S. Pat. No. 4,868,105
U.S. Pat. No. 5,252,479
EPO Publication No. 225,807
European Patent Application Publication No. 0332435
Geysen, H., PCT published application WO 84/03564, published 13 Sep. 1984
Hitzeman et al., EP 73,675A
PCT published application WO 93/07282

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i i i) NUMBER OF SEQUENCES: 85

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5914 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: cDNA

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(i x) FEATURE:
(A) NAME/KEY: CDS

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( B ) LOCATION: 120..5711

( x i ) SEQUENCE DESCRIPTION: SEQ ID NO:1:

AGCTCGCTGA GACTTCCTGG ACCCCGCACC AGGCTGTGGG GTTTCTCAGA TAACTGGGCC      60

CCTGCGCTCA GGAGGCCTTC ACCCTCTGCT CTGGGTAAAG TTCATTGGAA CAGAAAGAA      119

ATG GAT TTA TCT GCT CTT CGC GTT GAA GAA GTA CAA AAT GTC ATT AAT      167
Met Asp Leu Ser Ala Leu Arg Val Glu Glu Val Gln Asn Val Ile Asn
  1               5                  10                  15

GCT ATG CAG AAA ATC TTA GAG TGT CCC ATC TGT CTG GAG TTG ATC AAG      215
Ala Met Gln Lys Ile Leu Glu Cys Pro Ile Cys Leu Glu Leu Ile Lys
             20                  25                  30

GAA CCT GTC TCC ACA AAG TGT GAC CAC ATA TTT TGC AAA TTT TGC ATG      263
Glu Pro Val Ser Thr Lys Cys Asp His Ile Phe Cys Lys Phe Cys Met
         35                  40                  45

CTG AAA CTT CTC AAC CAG AAG AAA GGG CCT TCA CAG TGT CCT TTA TGT      311
Leu Lys Leu Leu Asn Gln Lys Lys Gly Pro Ser Gln Cys Pro Leu Cys
     50                  55                  60

AAG AAT GAT ATA ACC AAA AGG AGC CTA CAA GAA AGT ACG AGA TTT AGT      359
Lys Asn Asp Ile Thr Lys Arg Ser Leu Gln Glu Ser Thr Arg Phe Ser
 65                  70                  75                  80

CAA CTT GTT GAA GAG CTA TTG AAA ATC ATT TGT GCT TTT CAG CTT GAC      407
Gln Leu Val Glu Glu Leu Leu Lys Ile Ile Cys Ala Phe Gln Leu Asp
                 85                  90                  95

ACA GGT TTG GAG TAT GCA AAC AGC TAT AAT TTT GCA AAA AAG GAA AAT      455
Thr Gly Leu Glu Tyr Ala Asn Ser Tyr Asn Phe Ala Lys Lys Glu Asn
            100                 105                 110

AAC TCT CCT GAA CAT CTA AAA GAT GAA GTT TCT ATC ATC CAA AGT ATG      503
Asn Ser Pro Glu His Leu Lys Asp Glu Val Ser Ile Ile Gln Ser Met
        115                 120                 125

GGC TAC AGA AAC CGT GCC AAA AGA CTT CTA CAG AGT GAA CCC GAA AAT      551
Gly Tyr Arg Asn Arg Ala Lys Arg Leu Leu Gln Ser Glu Pro Glu Asn
    130                 135                 140

CCT TCC TTG CAG GAA ACC AGT CTC AGT GTC CAA CTC TCT AAC CTT GGA      599
Pro Ser Leu Gln Glu Thr Ser Leu Ser Val Gln Leu Ser Asn Leu Gly
145                 150                 155                 160

ACT GTG AGA ACT CTG AGG ACA AAG CAG CGG ATA CAA CCT CAA AAG ACG      647
Thr Val Arg Thr Leu Arg Thr Lys Gln Arg Ile Gln Pro Gln Lys Thr
                165                 170                 175

TCT GTC TAC ATT GAA TTG GGA TCT GAT TCT TCT GAA GAT ACC GTT AAT      695
Ser Val Tyr Ile Glu Leu Gly Ser Asp Ser Ser Glu Asp Thr Val Asn
            180                 185                 190

AAG GCA ACT TAT TGC AGT GTG GGA GAT CAA GAA TTG TTA CAA ATC ACC      743
Lys Ala Thr Tyr Cys Ser Val Gly Asp Gln Glu Leu Leu Gln Ile Thr
        195                 200                 205

CCT CAA GGA ACC AGG GAT GAA ATC AGT TTG GAT TCT GCA AAA AAG GCT      791
Pro Gln Gly Thr Arg Asp Glu Ile Ser Leu Asp Ser Ala Lys Lys Ala
    210                 215                 220

GCT TGT GAA TTT TCT GAG ACG GAT GTA ACA AAT ACT GAA CAT CAT CAA      839
Ala Cys Glu Phe Ser Glu Thr Asp Val Thr Asn Thr Glu His His Gln
225                 230                 235                 240

CCC AGT AAT AAT GAT TTG AAC ACC ACT GAG AAG CGT GCA GCT GAG AGG      887
Pro Ser Asn Asn Asp Leu Asn Thr Thr Glu Lys Arg Ala Ala Glu Arg
                245                 250                 255

CAT CCA GAA AAG TAT CAG GGT AGT TCT GTT TCA AAC TTG CAT GTG GAG      935
His Pro Glu Lys Tyr Gln Gly Ser Ser Val Ser Asn Leu His Val Glu
            260                 265                 270

CCA TGT GGC ACA AAT ACT CAT GCC AGC TCA TTA CAG CAT GAG AAC AGC      983
Pro Cys Gly Thr Asn Thr His Ala Ser Ser Leu Gln His Glu Asn Ser
        275                 280                 285
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AGT TTA TTA CTC ACT AAA GAC AGA ATG AAT GTA GAA AAG GCT GAA TTC        1031
Ser Leu Leu Leu Thr Lys Asp Arg Met Asn Val Glu Lys Ala Glu Phe
    290                 295                 300

TGT AAT AAA AGC AAA CAG CCT GGC TTA GCA AGG AGC CAA CAT AAC AGA        1079
Cys Asn Lys Ser Lys Gln Pro Gly Leu Ala Arg Ser Gln His Asn Arg
305                 310                 315                 320

TGG GCT GGA AGT AAG GAA ACA TGT AAT GAT AGG CGG ACT CCC AGC ACA        1127
Trp Ala Gly Ser Lys Glu Thr Cys Asn Asp Arg Arg Thr Pro Ser Thr
                325                 330                 335

GAA AAA AAG GTA GAT CTG AAT GCT GAT CCC CTG TGT GAG AGA AAA GAA        1175
Glu Lys Lys Val Asp Leu Asn Ala Asp Pro Leu Cys Glu Arg Lys Glu
            340                 345                 350

TGG AAT AAG CAG AAA CTG CCA TGC TCA GAG AAT CCT AGA GAT ACT GAA        1223
Trp Asn Lys Gln Lys Leu Pro Cys Ser Glu Asn Pro Arg Asp Thr Glu
        355                 360                 365

GAT GTT CCT TGG ATA ACA CTA AAT AGC AGC ATT CAG AAA GTT AAT GAG        1271
Asp Val Pro Trp Ile Thr Leu Asn Ser Ser Ile Gln Lys Val Asn Glu
    370                 375                 380

TGG TTT TCC AGA AGT GAT GAA CTG TTA GGT TCT GAT GAC TCA CAT GAT        1319
Trp Phe Ser Arg Ser Asp Glu Leu Leu Gly Ser Asp Asp Ser His Asp
385                 390                 395                 400

GGG GAG TCT GAA TCA AAT GCC AAA GTA GCT GAT GTA TTG GAC GTT CTA        1367
Gly Glu Ser Glu Ser Asn Ala Lys Val Ala Asp Val Leu Asp Val Leu
                405                 410                 415

AAT GAG GTA GAT GAA TAT TCT GGT TCT TCA GAG AAA ATA GAC TTA CTG        1415
Asn Glu Val Asp Glu Tyr Ser Gly Ser Ser Glu Lys Ile Asp Leu Leu
            420                 425                 430

GCC AGT GAT CCT CAT GAG GCT TTA ATA TGT AAA AGT GAA AGA GTT CAC        1463
Ala Ser Asp Pro His Glu Ala Leu Ile Cys Lys Ser Glu Arg Val His
        435                 440                 445

TCC AAA TCA GTA GAG AGT AAT ATT GAA GAC AAA ATA TTT GGG AAA ACC        1511
Ser Lys Ser Val Glu Ser Asn Ile Glu Asp Lys Ile Phe Gly Lys Thr
    450                 455                 460

TAT CGG AAG AAG GCA AGC CTC CCC AAC TTA AGC CAT GTA ACT GAA AAT        1559
Tyr Arg Lys Lys Ala Ser Leu Pro Asn Leu Ser His Val Thr Glu Asn
465                 470                 475                 480

CTA ATT ATA GGA GCA TTT GTT ACT GAG CCA CAG ATA ATA CAA GAG CGT        1607
Leu Ile Ile Gly Ala Phe Val Thr Glu Pro Gln Ile Ile Gln Glu Arg
                485                 490                 495

CCC CTC ACA AAT AAA TTA AAG CGT AAA AGG AGA CCT ACA TCA GGC CTT        1655
Pro Leu Thr Asn Lys Leu Lys Arg Lys Arg Arg Pro Thr Ser Gly Leu
            500                 505                 510

CAT CCT GAG GAT TTT ATC AAG AAA GCA GAT TTG GCA GTT CAA AAG ACT        1703
His Pro Glu Asp Phe Ile Lys Lys Ala Asp Leu Ala Val Gln Lys Thr
        515                 520                 525

CCT GAA ATG ATA AAT CAG GGA ACT AAC CAA ACG GAG CAG AAT GGT CAA        1751
Pro Glu Met Ile Asn Gln Gly Thr Asn Gln Thr Glu Gln Asn Gly Gln
    530                 535                 540

GTG ATG AAT ATT ACT AAT AGT GGT CAT GAG AAT AAA ACA AAA GGT GAT        1799
Val Met Asn Ile Thr Asn Ser Gly His Glu Asn Lys Thr Lys Gly Asp
545                 550                 555                 560

TCT ATT CAG AAT GAG AAA AAT CCT AAC CCA ATA GAA TCA CTC GAA AAA        1847
Ser Ile Gln Asn Glu Lys Asn Pro Asn Pro Ile Glu Ser Leu Glu Lys
                565                 570                 575

GAA TCT GCT TTC AAA ACG AAA GCT GAA CCT ATA AGC AGC AGT ATA AGC        1895
Glu Ser Ala Phe Lys Thr Lys Ala Glu Pro Ile Ser Ser Ser Ile Ser
            580                 585                 590

AAT ATG GAA CTC GAA TTA AAT ATC CAC AAT TCA AAA GCA CCT AAA AAG        1943
Asn Met Glu Leu Glu Leu Asn Ile His Asn Ser Lys Ala Pro Lys Lys
        595                 600                 605
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AAT AGG CTG AGG AGG AAG TCT TCT ACC AGG CAT ATT CAT GCG CTT GAA     1991
Asn Arg Leu Arg Arg Lys Ser Ser Thr Arg His Ile His Ala Leu Glu
    610                 615                 620

CTA GTA GTC AGT AGA AAT CTA AGC CCA CCT AAT TGT ACT GAA TTG CAA     2039
Leu Val Val Ser Arg Asn Leu Ser Pro Pro Asn Cys Thr Glu Leu Gln
625                 630                 635                 640

ATT GAT AGT TGT TCT AGC AGT GAA GAG ATA AAG AAA AAA AAG TAC AAC     2087
Ile Asp Ser Cys Ser Ser Ser Glu Glu Ile Lys Lys Lys Lys Tyr Asn
                645                 650                 655

CAA ATG CCA GTC AGG CAC AGC AGA AAC CTA CAA CTC ATG GAA GGT AAA     2135
Gln Met Pro Val Arg His Ser Arg Asn Leu Gln Leu Met Glu Gly Lys
            660                 665                 670

GAA CCT GCA ACT GGA GCC AAG AAG AGT AAC AAG CCA AAT GAA CAG ACA     2183
Glu Pro Ala Thr Gly Ala Lys Lys Ser Asn Lys Pro Asn Glu Gln Thr
        675                 680                 685

AGT AAA AGA CAT GAC AGC GAT ACT TTC CCA GAG CTG AAG TTA ACA AAT     2231
Ser Lys Arg His Asp Ser Asp Thr Phe Pro Glu Leu Lys Leu Thr Asn
    690                 695                 700

GCA CCT GGT TCT TTT ACT AAG TGT TCA AAT ACC AGT GAA CTT AAA GAA     2279
Ala Pro Gly Ser Phe Thr Lys Cys Ser Asn Thr Ser Glu Leu Lys Glu
705                 710                 715                 720

TTT GTC AAT CCT AGC CTT CCA AGA GAA GAA AAA GAA GAG AAA CTA GAA     2327
Phe Val Asn Pro Ser Leu Pro Arg Glu Glu Lys Glu Glu Lys Leu Glu
                725                 730                 735

ACA GTT AAA GTG TCT AAT AAT GCT GAA GAC CCC AAA GAT CTC ATG TTA     2375
Thr Val Lys Val Ser Asn Asn Ala Glu Asp Pro Lys Asp Leu Met Leu
            740                 745                 750

AGT GGA GAA AGG GTT TTG CAA ACT GAA AGA TCT GTA GAG AGT AGC AGT     2423
Ser Gly Glu Arg Val Leu Gln Thr Glu Arg Ser Val Glu Ser Ser Ser
        755                 760                 765

ATT TCA TTG GTA CCT GGT ACT GAT TAT GGC ACT CAG GAA AGT ATC TCG     2471
Ile Ser Leu Val Pro Gly Thr Asp Tyr Gly Thr Gln Glu Ser Ile Ser
    770                 775                 780

TTA CTG GAA GTT AGC ACT CTA GGG AAG GCA AAA ACA GAA CCA AAT AAA     2519
Leu Leu Glu Val Ser Thr Leu Gly Lys Ala Lys Thr Glu Pro Asn Lys
785                 790                 795                 800

TGT GTG AGT CAG TGT GCA GCA TTT GAA AAC CCC AAG GGA CTA ATT CAT     2567
Cys Val Ser Gln Cys Ala Ala Phe Glu Asn Pro Lys Gly Leu Ile His
                805                 810                 815

GGT TGT TCC AAA GAT AAT AGA AAT GAC ACA GAA GGC TTT AAG TAT CCA     2615
Gly Cys Ser Lys Asp Asn Arg Asn Asp Thr Glu Gly Phe Lys Tyr Pro
            820                 825                 830

TTG GGA CAT GAA GTT AAC CAC AGT CGG GAA ACA AGC ATA GAA ATG GAA     2663
Leu Gly His Glu Val Asn His Ser Arg Glu Thr Ser Ile Glu Met Glu
        835                 840                 845

GAA AGT GAA CTT GAT GCT CAG TAT TTG CAG AAT ACA TTC AAG GTT TCA     2711
Glu Ser Glu Leu Asp Ala Gln Tyr Leu Gln Asn Thr Phe Lys Val Ser
    850                 855                 860

AAG CGC CAG TCA TTT GCT CCG TTT TCA AAT CCA GGA AAT GCA GAA GAG     2759
Lys Arg Gln Ser Phe Ala Pro Phe Ser Asn Pro Gly Asn Ala Glu Glu
865                 870                 875                 880

GAA TGT GCA ACA TTC TCT GCC CAC TCT GGG TCC TTA AAG AAA CAA AGT     2807
Glu Cys Ala Thr Phe Ser Ala His Ser Gly Ser Leu Lys Lys Gln Ser
                885                 890                 895

CCA AAA GTC ACT TTT GAA TGT GAA CAA AAG GAA GAA AAT CAA GGA AAG     2855
Pro Lys Val Thr Phe Glu Cys Glu Gln Lys Glu Glu Asn Gln Gly Lys
            900                 905                 910

AAT GAG TCT AAT ATC AAG CCT GTA CAG ACA GTT AAT ATC ACT GCA GGC     2903
Asn Glu Ser Asn Ile Lys Pro Val Gln Thr Val Asn Ile Thr Ala Gly
        915                 920                 925
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TTT CCT GTG GTT GGT CAG AAA GAT AAG CCA GTT GAT AAT GCC AAA TGT       2951
Phe Pro Val Val Gly Gln Lys Asp Lys Pro Val Asp Asn Ala Lys Cys
    930                 935                 940

AGT ATC AAA GGA GGC TCT AGG TTT TGT CTA TCA TCT CAG TTC AGA GGC       2999
Ser Ile Lys Gly Gly Ser Arg Phe Cys Leu Ser Ser Gln Phe Arg Gly
945                 950                 955                 960

AAC GAA ACT GGA CTC ATT ACT CCA AAT AAA CAT GGA CTT TTA CAA AAC       3047
Asn Glu Thr Gly Leu Ile Thr Pro Asn Lys His Gly Leu Leu Gln Asn
                965                 970                 975

CCA TAT CGT ATA CCA CCA CTT TTT CCC ATC AAG TCA TTT GTT AAA ACT       3095
Pro Tyr Arg Ile Pro Pro Leu Phe Pro Ile Lys Ser Phe Val Lys Thr
            980                 985                 990

AAA TGT AAG AAA AAT CTG CTA GAG GAA AAC TTT GAG GAA CAT TCA ATG       3143
Lys Cys Lys Lys Asn Leu Leu Glu Glu Asn Phe Glu Glu His Ser Met
        995                1000                1005

TCA CCT GAA AGA GAA ATG GGA AAT GAG AAC ATT CCA AGT ACA GTG AGC       3191
Ser Pro Glu Arg Glu Met Gly Asn Glu Asn Ile Pro Ser Thr Val Ser
    1010                1015                1020

ACA ATT AGC CGT AAT AAC ATT AGA GAA AAT GTT TTT AAA GAA GCC AGC       3239
Thr Ile Ser Arg Asn Asn Ile Arg Glu Asn Val Phe Lys Glu Ala Ser
1025                1030                1035                1040

TCA AGC AAT ATT AAT GAA GTA GGT TCC AGT ACT AAT GAA GTG GGC TCC       3287
Ser Ser Asn Ile Asn Glu Val Gly Ser Ser Thr Asn Glu Val Gly Ser
                1045                1050                1055

AGT ATT AAT GAA ATA GGT TCC AGT GAT GAA AAC ATT CAA GCA GAA CTA       3335
Ser Ile Asn Glu Ile Gly Ser Ser Asp Glu Asn Ile Gln Ala Glu Leu
            1060                1065                1070

GGT AGA AAC AGA GGG CCA AAA TTG AAT GCT ATG CTT AGA TTA GGG GTT       3383
Gly Arg Asn Arg Gly Pro Lys Leu Asn Ala Met Leu Arg Leu Gly Val
        1075                1080                1085

TTG CAA CCT GAG GTC TAT AAA CAA AGT CTT CCT GGA AGT AAT TGT AAG       3431
Leu Gln Pro Glu Val Tyr Lys Gln Ser Leu Pro Gly Ser Asn Cys Lys
    1090                1095                1100

CAT CCT GAA ATA AAA AAG CAA GAA TAT GAA GAA GTA GTT CAG ACT GTT       3479
His Pro Glu Ile Lys Lys Gln Glu Tyr Glu Glu Val Val Gln Thr Val
1105                1110                1115                1120

AAT ACA GAT TTC TCT CCA TAT CTG ATT TCA GAT AAC TTA GAA CAG CCT       3527
Asn Thr Asp Phe Ser Pro Tyr Leu Ile Ser Asp Asn Leu Glu Gln Pro
                1125                1130                1135

ATG GGA AGT AGT CAT GCA TCT CAG GTT TGT TCT GAG ACA CCT GAT GAC       3575
Met Gly Ser Ser His Ala Ser Gln Val Cys Ser Glu Thr Pro Asp Asp
            1140                1145                1150

CTG TTA GAT GAT GGT GAA ATA AAG GAA GAT ACT AGT TTT GCT GAA AAT       3623
Leu Leu Asp Asp Gly Glu Ile Lys Glu Asp Thr Ser Phe Ala Glu Asn
        1155                1160                1165

GAC ATT AAG GAA AGT TCT GCT GTT TTT AGC AAA AGC GTC CAG AAA GGA       3671
Asp Ile Lys Glu Ser Ser Ala Val Phe Ser Lys Ser Val Gln Lys Gly
    1170                1175                1180

GAG CTT AGC AGG AGT CCT AGC CCT TTC ACC CAT ACA CAT TTG GCT CAG       3719
Glu Leu Ser Arg Ser Pro Ser Pro Phe Thr His Thr His Leu Ala Gln
1185                1190                1195                1200

GGT TAC CGA AGA GGG GCC AAG AAA TTA GAG TCC TCA GAA GAG AAC TTA       3767
Gly Tyr Arg Arg Gly Ala Lys Lys Leu Glu Ser Ser Glu Glu Asn Leu
                1205                1210                1215

TCT AGT GAG GAT GAA GAG CTT CCC TGC TTC CAA CAC TTG TTA TTT GGT       3815
Ser Ser Glu Asp Glu Glu Leu Pro Cys Phe Gln His Leu Leu Phe Gly
            1220                1225                1230

AAA GTA AAC AAT ATA CCT TCT CAG TCT ACT AGG CAT AGC ACC GTT GCT       3863
Lys Val Asn Asn Ile Pro Ser Gln Ser Thr Arg His Ser Thr Val Ala
        1235                1240                1245
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ACC GAG TGT CTG TCT AAG AAC ACA GAG GAG AAT TTA TTA TCA TTG AAG     3911
Thr Glu Cys Leu Ser Lys Asn Thr Glu Glu Asn Leu Leu Ser Leu Lys
    1250                1255                1260

AAT AGC TTA AAT GAC TGC AGT AAC CAG GTA ATA TTG GCA AAG GCA TCT     3959
Asn Ser Leu Asn Asp Cys Ser Asn Gln Val Ile Leu Ala Lys Ala Ser
1265                1270                1275                1280

CAG GAA CAT CAC CTT AGT GAG GAA ACA AAA TGT TCT GCT AGC TTG TTT     4007
Gln Glu His His Leu Ser Glu Glu Thr Lys Cys Ser Ala Ser Leu Phe
                1285                1290                1295

TCT TCA CAG TGC AGT GAA TTG GAA GAC TTG ACT GCA AAT ACA AAC ACC     4055
Ser Ser Gln Cys Ser Glu Leu Glu Asp Leu Thr Ala Asn Thr Asn Thr
            1300                1305                1310

CAG GAT CCT TTC TTG ATT GGT TCT TCC AAA CAA ATG AGG CAT CAG TCT     4103
Gln Asp Pro Phe Leu Ile Gly Ser Ser Lys Gln Met Arg His Gln Ser
        1315                1320                1325

GAA AGC CAG GGA GTT GGT CTG AGT GAC AAG GAA TTG GTT TCA GAT GAT     4151
Glu Ser Gln Gly Val Gly Leu Ser Asp Lys Glu Leu Val Ser Asp Asp
    1330                1335                1340

GAA GAA AGA GGA ACG GGC TTG GAA GAA AAT AAT CAA GAA GAG CAA AGC     4199
Glu Glu Arg Gly Thr Gly Leu Glu Glu Asn Asn Gln Glu Glu Gln Ser
1345                1350                1355                1360

ATG GAT TCA AAC TTA GGT GAA GCA GCA TCT GGG TGT GAG AGT GAA ACA     4247
Met Asp Ser Asn Leu Gly Glu Ala Ala Ser Gly Cys Glu Ser Glu Thr
                1365                1370                1375

AGC GTC TCT GAA GAC TGC TCA GGG CTA TCC TCT CAG AGT GAC ATT TTA     4295
Ser Val Ser Glu Asp Cys Ser Gly Leu Ser Ser Gln Ser Asp Ile Leu
            1380                1385                1390

ACC ACT CAG CAG AGG GAT ACC ATG CAA CAT AAC CTG ATA AAG CTC CAG     4343
Thr Thr Gln Gln Arg Asp Thr Met Gln His Asn Leu Ile Lys Leu Gln
        1395                1400                1405

CAG GAA ATG GCT GAA CTA GAA GCT GTG TTA GAA CAG CAT GGG AGC CAG     4391
Gln Glu Met Ala Glu Leu Glu Ala Val Leu Glu Gln His Gly Ser Gln
    1410                1415                1420

CCT TCT AAC AGC TAC CCT TCC ATC ATA AGT GAC TCT TCT GCC CTT GAG     4439
Pro Ser Asn Ser Tyr Pro Ser Ile Ile Ser Asp Ser Ser Ala Leu Glu
1425                1430                1435                1440

GAC CTG CGA AAT CCA GAA CAA AGC ACA TCA GAA AAA GCA GTA TTA ACT     4487
Asp Leu Arg Asn Pro Glu Gln Ser Thr Ser Glu Lys Ala Val Leu Thr
                1445                1450                1455

TCA CAG AAA AGT AGT GAA TAC CCT ATA AGC CAG AAT CCA GAA GGC CTT     4535
Ser Gln Lys Ser Ser Glu Tyr Pro Ile Ser Gln Asn Pro Glu Gly Leu
            1460                1465                1470

TCT GCT GAC AAG TTT GAG GTG TCT GCA GAT AGT TCT ACC AGT AAA AAT     4583
Ser Ala Asp Lys Phe Glu Val Ser Ala Asp Ser Ser Thr Ser Lys Asn
        1475                1480                1485

AAA GAA CCA GGA GTG GAA AGG TCA TCC CCT TCT AAA TGC CCA TCA TTA     4631
Lys Glu Pro Gly Val Glu Arg Ser Ser Pro Ser Lys Cys Pro Ser Leu
    1490                1495                1500

GAT GAT AGG TGG TAC ATG CAC AGT TGC TCT GGG AGT CTT CAG AAT AGA     4679
Asp Asp Arg Trp Tyr Met His Ser Cys Ser Gly Ser Leu Gln Asn Arg
1505                1510                1515                1520

AAC TAC CCA TCT CAA GAG GAG CTC ATT AAG GTT GTT GAT GTG GAG GAG     4727
Asn Tyr Pro Ser Gln Glu Glu Leu Ile Lys Val Val Asp Val Glu Glu
                1525                1530                1535

CAA CAG CTG GAA GAG TCT GGG CCA CAC GAT TTG ACG GAA ACA TCT TAC     4775
Gln Gln Leu Glu Glu Ser Gly Pro His Asp Leu Thr Glu Thr Ser Tyr
            1540                1545                1550

TTG CCA AGG CAA GAT CTA GAG GGA ACC CCT TAC CTG GAA TCT GGA ATC     4823
Leu Pro Arg Gln Asp Leu Glu Gly Thr Pro Tyr Leu Glu Ser Gly Ile
        1555                1560                1565
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AGC CTC TTC TCT GAT GAC CCT GAA TCT GAT CCT TCT GAA GAC AGA GCC       4871
Ser Leu Phe Ser Asp Asp Pro Glu Ser Asp Pro Ser Glu Asp Arg Ala
    1570                1575                1580

CCA GAG TCA GCT CGT GTT GGC AAC ATA CCA TCT TCA ACC TCT GCA TTG       4919
Pro Glu Ser Ala Arg Val Gly Asn Ile Pro Ser Ser Thr Ser Ala Leu
1585                1590                1595                1600

AAA GTT CCC CAA TTG AAA GTT GCA GAA TCT GCC CAG AGT CCA GCT GCT       4967
Lys Val Pro Gln Leu Lys Val Ala Glu Ser Ala Gln Ser Pro Ala Ala
                1605                1610                1615

GCT CAT ACT ACT GAT ACT GCT GGG TAT AAT GCA ATG GAA GAA AGT GTG       5015
Ala His Thr Thr Asp Thr Ala Gly Tyr Asn Ala Met Glu Glu Ser Val
            1620                1625                1630

AGC AGG GAG AAG CCA GAA TTG ACA GCT TCA ACA GAA AGG GTC AAC AAA       5063
Ser Arg Glu Lys Pro Glu Leu Thr Ala Ser Thr Glu Arg Val Asn Lys
        1635                1640                1645

AGA ATG TCC ATG GTG GTG TCT GGC CTG ACC CCA GAA GAA TTT ATG CTC       5111
Arg Met Ser Met Val Val Ser Gly Leu Thr Pro Glu Glu Phe Met Leu
    1650                1655                1660

GTG TAC AAG TTT GCC AGA AAA CAC CAC ATC ACT TTA ACT AAT CTA ATT       5159
Val Tyr Lys Phe Ala Arg Lys His His Ile Thr Leu Thr Asn Leu Ile
1665                1670                1675                1680

ACT GAA GAG ACT ACT CAT GTT GTT ATG AAA ACA GAT GCT GAG TTT GTG       5207
Thr Glu Glu Thr Thr His Val Val Met Lys Thr Asp Ala Glu Phe Val
                1685                1690                1695

TGT GAA CGG ACA CTG AAA TAT TTT CTA GGA ATT GCG GGA GGA AAA TGG       5255
Cys Glu Arg Thr Leu Lys Tyr Phe Leu Gly Ile Ala Gly Gly Lys Trp
            1700                1705                1710

GTA GTT AGC TAT TTC TGG GTG ACC CAG TCT ATT AAA GAA AGA AAA ATG       5303
Val Val Ser Tyr Phe Trp Val Thr Gln Ser Ile Lys Glu Arg Lys Met
        1715                1720                1725

CTG AAT GAG CAT GAT TTT GAA GTC AGA GGA GAT GTG GTC AAT GGA AGA       5351
Leu Asn Glu His Asp Phe Glu Val Arg Gly Asp Val Val Asn Gly Arg
    1730                1735                1740

AAC CAC CAA GGT CCA AAG CGA GCA AGA GAA TCC CAG GAC AGA AAG ATC       5399
Asn His Gln Gly Pro Lys Arg Ala Arg Glu Ser Gln Asp Arg Lys Ile
1745                1750                1755                1760

TTC AGG GGG CTA GAA ATC TGT TGC TAT GGG CCC TTC ACC AAC ATG CCC       5447
Phe Arg Gly Leu Glu Ile Cys Cys Tyr Gly Pro Phe Thr Asn Met Pro
                1765                1770                1775

ACA GAT CAA CTG GAA TGG ATG GTA CAG CTG TGT GGT GCT TCT GTG GTG       5495
Thr Asp Gln Leu Glu Trp Met Val Gln Leu Cys Gly Ala Ser Val Val
            1780                1785                1790

AAG GAG CTT TCA TCA TTC ACC CTT GGC ACA GGT GTC CAC CCA ATT GTG       5543
Lys Glu Leu Ser Ser Phe Thr Leu Gly Thr Gly Val His Pro Ile Val
        1795                1800                1805

GTT GTG CAG CCA GAT GCC TGG ACA GAG GAC AAT GGC TTC CAT GCA ATT       5591
Val Val Gln Pro Asp Ala Trp Thr Glu Asp Asn Gly Phe His Ala Ile
    1810                1815                1820

GGG CAG ATG TGT GAG GCA CCT GTG GTG ACC CGA GAG TGG GTG TTG GAC       5639
Gly Gln Met Cys Glu Ala Pro Val Val Thr Arg Glu Trp Val Leu Asp
1825                1830                1835                1840

AGT GTA GCA CTC TAC CAG TGC CAG GAG CTG GAC ACC TAC CTG ATA CCC       5687
Ser Val Ala Leu Tyr Gln Cys Gln Glu Leu Asp Thr Tyr Leu Ile Pro
                1845                1850                1855

CAG ATC CCC CAC AGC CAC TAC TGA CTGCAGCCAG CCACAGGTAC AGAGCCACAG      5741
Gln Ile Pro His Ser His Tyr  *
            1860

GACCCCAAGA ATGAGCTTAC AAAGTGGCCT TTCCAGGCCC TGGGAGCTCC TCTCACTCTT     5801

CAGTCCTTCT ACTGTCCTGG CTACTAAATA TTTTATGTAC ATCAGCCTGA AAAGGACTTC     5861
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TGGCTATGCA AGGGTCCCTT AAAGATTTTC TGCTTGAAGT CTCCCTTGGA AAT 5914

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1863 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: protein

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Asp Leu Ser Ala Leu Arg Val Glu Glu Val Gln Asn Val Ile Asn
1 5 10 15

Ala Met Gln Lys Ile Leu Glu Cys Pro Ile Cys Leu Glu Leu Ile Lys
20 25 30

Glu Pro Val Ser Thr Lys Cys Asp His Ile Phe Cys Lys Phe Cys Met
35 40 45

Leu Lys Leu Leu Asn Gln Lys Lys Gly Pro Ser Gln Cys Pro Leu Cys
50 55 60

Lys Asn Asp Ile Thr Lys Arg Ser Leu Gln Glu Ser Thr Arg Phe Ser
65 70 75 80

Gln Leu Val Glu Glu Leu Leu Lys Ile Ile Cys Ala Phe Gln Leu Asp
85 90 95

Thr Gly Leu Glu Tyr Ala Asn Ser Tyr Asn Phe Ala Lys Lys Glu Asn
100 105 110

Asn Ser Pro Glu His Leu Lys Asp Glu Val Ser Ile Ile Gln Ser Met
115 120 125

Gly Tyr Arg Asn Arg Ala Lys Arg Leu Leu Gln Ser Glu Pro Glu Asn
130 135 140

Pro Ser Leu Gln Glu Thr Ser Leu Ser Val Gln Leu Ser Asn Leu Gly
145 150 155 160

Thr Val Arg Thr Leu Arg Thr Lys Gln Arg Ile Gln Pro Gln Lys Thr
165 170 175

Ser Val Tyr Ile Glu Leu Gly Ser Asp Ser Ser Glu Asp Thr Val Asn
180 185 190

Lys Ala Thr Tyr Cys Ser Val Gly Asp Gln Glu Leu Leu Gln Ile Thr
195 200 205

Pro Gln Gly Thr Arg Asp Glu Ile Ser Leu Asp Ser Ala Lys Lys Ala
210 215 220

Ala Cys Glu Phe Ser Glu Thr Asp Val Thr Asn Thr Glu His His Gln
225 230 235 240

Pro Ser Asn Asn Asp Leu Asn Thr Thr Glu Lys Arg Ala Ala Glu Arg
245 250 255

His Pro Glu Lys Tyr Gln Gly Ser Ser Val Ser Asn Leu His Val Glu
260 265 270

Pro Cys Gly Thr Asn Thr His Ala Ser Ser Leu Gln His Glu Asn Ser
275 280 285

Ser Leu Leu Leu Thr Lys Asp Arg Met Asn Val Glu Lys Ala Glu Phe
290 295 300

Cys Asn Lys Ser Lys Gln Pro Gly Leu Ala Arg Ser Gln His Asn Arg
305 310 315 320

Trp Ala Gly Ser Lys Glu Thr Cys Asn Asp Arg Arg Thr Pro Ser Thr
325 330 335

Glu Lys Lys Val Asp Leu Asn Ala Asp Pro Leu Cys Glu Arg Lys Glu
340 345 350

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Trp Asn Lys Gln Lys Leu Pro Cys Ser Glu Asn Pro Arg Asp Thr Glu
        355                 360                 365

Asp Val Pro Trp Ile Thr Leu Asn Ser Ser Ile Gln Lys Val Asn Glu
    370                 375                 380

Trp Phe Ser Arg Ser Asp Glu Leu Leu Gly Ser Asp Asp Ser His Asp
385                 390                 395                 400

Gly Gln Ser Glu Ser Asn Ala Lys Val Ala Asp Val Leu Asp Val Leu
                405                 410                 415

Asn Glu Val Asp Gln Tyr Ser Gly Ser Ser Glu Lys Ile Asp Leu Leu
            420                 425                 430

Ala Ser Asp Pro His Gln Ala Leu Ile Cys Lys Ser Glu Arg Val His
        435                 440                 445

Ser Lys Ser Val Glu Ser Asn Ile Glu Asp Lys Ile Phe Gly Lys Thr
    450                 455                 460

Tyr Arg Lys Lys Ala Ser Leu Pro Asn Leu Ser His Val Thr Glu Asn
465                 470                 475                 480

Leu Ile Ile Gly Ala Phe Val Thr Glu Pro Gln Ile Ile Gln Glu Arg
                485                 490                 495

Pro Leu Thr Asn Lys Leu Lys Arg Lys Arg Arg Pro Thr Ser Gly Leu
            500                 505                 510

His Pro Gln Asp Phe Ile Lys Lys Ala Asp Leu Ala Val Gln Lys Thr
        515                 520                 525

Pro Gln Met Ile Asn Gln Gly Thr Asn Gln Thr Glu Gln Asn Gly Gln
    530                 535                 540

Val Met Asn Ile Thr Asn Ser Gly His Glu Asn Lys Thr Lys Gly Asp
545                 550                 555                 560

Ser Ile Gln Asn Glu Lys Asn Pro Asn Pro Ile Gln Ser Leu Glu Lys
                565                 570                 575

Glu Ser Ala Phe Lys Thr Lys Ala Gln Pro Ile Ser Ser Ser Ile Ser
            580                 585                 590

Asn Met Glu Leu Glu Leu Asn Ile His Asn Ser Lys Ala Pro Lys Lys
        595                 600                 605

Asn Arg Leu Arg Arg Lys Ser Ser Thr Arg His Ile His Ala Leu Glu
    610                 615                 620

Leu Val Val Ser Arg Asn Leu Ser Pro Pro Asn Cys Thr Gln Leu Gln
625                 630                 635                 640

Ile Asp Ser Cys Ser Ser Ser Glu Glu Ile Lys Lys Lys Lys Tyr Asn
                645                 650                 655

Gln Met Pro Val Arg His Ser Arg Asn Leu Gln Leu Met Gln Gly Lys
            660                 665                 670

Glu Pro Ala Thr Gly Ala Lys Lys Ser Asn Lys Pro Asn Glu Gln Thr
        675                 680                 685

Ser Lys Arg His Asp Ser Asp Thr Phe Pro Glu Leu Lys Leu Thr Asn
    690                 695                 700

Ala Pro Gly Ser Phe Thr Lys Cys Ser Asn Thr Ser Glu Leu Lys Glu
705                 710                 715                 720

Phe Val Asn Pro Ser Leu Pro Arg Glu Glu Lys Glu Glu Lys Leu Glu
                725                 730                 735

Thr Val Lys Val Ser Asn Asn Ala Glu Asp Pro Lys Asp Leu Met Leu
            740                 745                 750

Ser Gly Gln Arg Val Leu Gln Thr Glu Arg Ser Val Gln Ser Ser Ser
        755                 760                 765

Ile Ser Leu Val Pro Gly Thr Asp Tyr Gly Thr Gln Glu Ser Ile Ser
    770                 775                 780
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Leu Leu Glu Val Ser Thr Leu Gly Lys Ala Lys Thr Gln Pro Asn Lys
785                 790                 795                 800

Cys Val Ser Gln Cys Ala Ala Phe Glu Asn Pro Lys Gly Leu Ile His
                805                 810                 815

Gly Cys Ser Lys Asp Asn Arg Asn Asp Thr Gln Gly Phe Lys Tyr Pro
            820                 825                 830

Leu Gly His Glu Val Asn His Ser Arg Glu Thr Ser Ile Gln Met Glu
        835                 840                 845

Gln Ser Glu Leu Asp Ala Gln Tyr Leu Gln Asn Thr Phe Lys Val Ser
    850                 855                 860

Lys Arg Gln Ser Phe Ala Pro Phe Ser Asn Pro Gly Asn Ala Glu Gln
865                 870                 875                 880

Gln Cys Ala Thr Phe Ser Ala His Ser Gly Ser Leu Lys Lys Gln Ser
                885                 890                 895

Pro Lys Val Thr Phe Glu Cys Glu Gln Lys Glu Glu Asn Gln Gly Lys
            900                 905                 910

Asn Gln Ser Asn Ile Lys Pro Val Gln Thr Val Asn Ile Thr Ala Gly
        915                 920                 925

Phe Pro Val Val Gly Gln Lys Asp Lys Pro Val Asp Asn Ala Lys Cys
    930                 935                 940

Ser Ile Lys Gly Gly Ser Arg Phe Cys Leu Ser Ser Gln Phe Arg Gly
945                 950                 955                 960

Asn Glu Thr Gly Leu Ile Thr Pro Asn Lys His Gly Leu Leu Gln Asn
                965                 970                 975

Pro Tyr Arg Ile Pro Pro Leu Phe Pro Ile Lys Ser Phe Val Lys Thr
            980                 985                 990

Lys Cys Lys Lys Asn Leu Leu Glu Glu Asn Phe Glu Glu His Ser Met
        995                 1000                1005

Ser Pro Gln Arg Glu Met Gly Asn Glu Asn Ile Pro Ser Thr Val Ser
    1010                1015                1020

Thr Ile Ser Arg Asn Asn Ile Arg Glu Asn Val Phe Lys Glu Ala Ser
1025                1030                1035                1040

Ser Ser Asn Ile Asn Glu Val Gly Ser Ser Thr Asn Glu Val Gly Ser
                1045                1050                1055

Ser Ile Asn Glu Ile Gly Ser Ser Asp Glu Asn Ile Gln Ala Gln Leu
            1060                1065                1070

Gly Arg Asn Arg Gly Pro Lys Leu Asn Ala Met Leu Arg Leu Gly Val
        1075                1080                1085

Leu Gln Pro Glu Val Tyr Lys Gln Ser Leu Pro Gly Ser Asn Cys Lys
    1090                1095                1100

His Pro Glu Ile Lys Lys Gln Glu Tyr Glu Glu Val Val Gln Thr Val
1105                1110                1115                1120

Asn Thr Asp Phe Ser Pro Tyr Leu Ile Ser Asp Asn Leu Glu Gln Pro
                1125                1130                1135

Met Gly Ser Ser His Ala Ser Gln Val Cys Ser Glu Thr Pro Asp Asp
            1140                1145                1150

Leu Leu Asp Asp Gly Glu Ile Lys Glu Asp Thr Ser Phe Ala Glu Asn
        1155                1160                1165

Asp Ile Lys Glu Ser Ser Ala Val Phe Ser Lys Ser Val Gln Lys Gly
    1170                1175                1180

Glu Leu Ser Arg Ser Pro Ser Pro Phe Thr His Thr His Leu Ala Gln
1185                1190                1195                1200

Gly Tyr Arg Arg Gly Ala Lys Lys Leu Glu Ser Ser Glu Glu Asn Leu
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                1205                1210                1215

Ser Ser Gln Asp Glu Gln Leu Pro Cys Phe Gln His Leu Leu Phe Gly
            1220                1225                1230

Lys Val Asn Asn Ile Pro Ser Gln Ser Thr Arg His Ser Thr Val Ala
        1235                1240                1245

Thr Glu Cys Leu Ser Lys Asn Thr Gln Glu Asn Leu Leu Ser Leu Lys
    1250                1255                1260

Asn Ser Leu Asn Asp Cys Ser Asn Gln Val Ile Leu Ala Lys Ala Ser
1265                1270                1275                1280

Gln Glu His His Leu Ser Glu Glu Thr Lys Cys Ser Ala Ser Leu Phe
                1285                1290                1295

Ser Ser Gln Cys Ser Gln Leu Glu Asp Leu Thr Ala Asn Thr Asn Thr
            1300                1305                1310

Gln Asp Pro Phe Leu Ile Gly Ser Ser Lys Gln Met Arg His Gln Ser
        1315                1320                1325

Glu Ser Gln Gly Val Gly Leu Ser Asp Lys Glu Leu Val Ser Asp Asp
    1330                1335                1340

Gln Glu Arg Gly Thr Gly Leu Gln Gln Asn Asn Gln Gln Glu Gln Ser
1345                1350                1355                1360

Met Asp Ser Asn Leu Gly Glu Ala Ala Ser Gly Cys Gln Ser Glu Thr
                1365                1370                1375

Ser Val Ser Glu Asp Cys Ser Gly Leu Ser Ser Gln Ser Asp Ile Leu
            1380                1385                1390

Thr Thr Gln Gln Arg Asp Thr Met Gln His Asn Leu Ile Lys Leu Gln
        1395                1400                1405

Gln Gln Met Ala Glu Leu Glu Ala Val Leu Glu Gln His Gly Ser Gln
    1410                1415                1420

Pro Ser Asn Ser Tyr Pro Ser Ile Ile Ser Asp Ser Ser Ala Leu Glu
1425                1430                1435                1440

Asp Leu Arg Asn Pro Glu Gln Ser Thr Ser Glu Lys Ala Val Leu Thr
                1445                1450                1455

Ser Gln Lys Ser Ser Glu Tyr Pro Ile Ser Gln Asn Pro Glu Gly Leu
            1460                1465                1470

Ser Ala Asp Lys Phe Glu Val Ser Ala Asp Ser Ser Thr Ser Lys Asn
        1475                1480                1485

Lys Glu Pro Gly Val Glu Arg Ser Ser Pro Ser Lys Cys Pro Ser Leu
    1490                1495                1500

Asp Asp Arg Trp Tyr Met His Ser Cys Ser Gly Ser Leu Gln Asn Arg
1505                1510                1515                1520

Asn Tyr Pro Ser Gln Gln Glu Leu Ile Lys Val Val Asp Val Glu Glu
                1525                1530                1535

Gln Gln Leu Glu Glu Ser Gly Pro His Asp Leu Thr Glu Thr Ser Tyr
            1540                1545                1550

Leu Pro Arg Gln Asp Leu Glu Gly Thr Pro Tyr Leu Glu Ser Gly Ile
        1555                1560                1565

Ser Leu Phe Ser Asp Asp Pro Glu Ser Asp Pro Ser Gln Asp Arg Ala
    1570                1575                1580

Pro Glu Ser Ala Arg Val Gly Asn Ile Pro Ser Ser Thr Ser Ala Leu
1585                1590                1595                1600

Lys Val Pro Gln Leu Lys Val Ala Glu Ser Ala Gln Ser Pro Ala Ala
                1605                1610                1615

Ala His Thr Thr Asp Thr Ala Gly Tyr Asn Ala Met Glu Glu Ser Val
            1620                1625                1630
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Ser Arg Glu Lys Pro Glu Leu Thr Ala Ser Thr Glu Arg Val Asn Lys
1635 1640 1645

Arg Met Ser Met Val Val Ser Gly Leu Thr Pro Glu Gln Phe Met Leu
1650 1655 1660

Val Tyr Lys Phe Ala Arg Lys His His Ile Thr Leu Thr Asn Leu Ile
1665 1670 1675 1680

Thr Gln Gln Thr Thr His Val Val Met Lys Thr Asp Ala Gln Phe Val
1685 1690 1695

Cys Gln Arg Thr Leu Lys Tyr Phe Leu Gly Ile Ala Gly Gly Lys Trp
1700 1705 1710

Val Val Ser Tyr Phe Trp Val Thr Gln Ser Ile Lys Glu Arg Lys Met
1715 1720 1725

Leu Asn Glu His Asp Phe Gln Val Arg Gly Asp Val Val Asn Gly Arg
1730 1735 1740

Asn His Gln Gly Pro Lys Arg Ala Arg Gln Ser Gln Asp Arg Lys Ile
1745 1750 1755 1760

Phe Arg Gly Leu Gln Ile Cys Cys Tyr Gly Pro Phe Thr Asn Met Pro
1765 1770 1775

Thr Asp Gln Leu Gln Trp Met Val Gln Leu Cys Gly Ala Ser Val Val
1780 1785 1790

Lys Glu Leu Ser Ser Phe Thr Leu Gly Thr Gly Val His Pro Ile Val
1795 1800 1805

Val Val Gln Pro Asp Ala Trp Thr Gln Asp Asn Gly Phe His Ala Ile
1810 1815 1820

Gly Gln Met Cys Glu Ala Pro Val Val Thr Arg Glu Trp Val Leu Asp
1825 1830 1835 1840

Ser Val Ala Leu Tyr Gln Cys Gln Glu Leu Asp Thr Tyr Leu Ile Pro
1845 1850 1855

Gln Ile Pro His Ser His Tyr
1860

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(v i i) IMMEDIATE SOURCE:
(B) CLONE: s754A

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CTAGCCTGGG CAACAAACGA 20

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

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(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(v i i) IMMEDIATE SOURCE:
(B) CLONE: s754 B

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:4:

GCAGGAAGCA GGAATGGAAC 20

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(v i i) IMMEDIATE SOURCE:
(B) CLONE: s975 A

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:5:

TAGGAGATGC ATTATTGGTG 20

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(v i i) IMMEDIATE SOURCE:
(B) CLONE: s975 B

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:6:

AGGCAACTTT GCAATGAGTG 20

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(v i i) IMMEDIATE SOURCE:
(B) CLONE: tdj1474 A

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CAGAGTGAGA CCTTGTCTCA AA 22

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(v i i) IMMEDIATE SOURCE:
(B) CLONE: stj1474 B

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:8:

TTCTGCAAAC ACCTTAAACT CAG 23

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(v i i) IMMEDIATE SOURCE:
(B) CLONE: stj1239 A

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:9:

AACCTGGAAG GCAGAGGTTG 20

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(v i i) IMMEDIATE SOURCE:
(B) CLONE: stj1239 B

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:10:

TCTGTACCTG CTAAGCAGTG G 21

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: cDNA

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(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(i x) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..111

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:11:

G GNC TTA CTC TGT TGT CCC AGC TGG AGT ACA GNG TGC GAT CAT GAG 46
Xaa Leu Leu Cys Cys Pro Ser Trp Ser Thr Xaa Cys Asp His Glu
1865 1870 1875

GCT TAC TGT TGC TTG ACT CCT AGG CTC AAG CGA TCC TAT CAC CTC AGT 94
Ala Tyr Cys Cys Leu Thr Pro Arg Leu Lys Arg Ser Tyr His Leu Ser
1880 1885 1890 1895

CTC CAA GTA GCT GGA CT 111
Leu Gln Val Ala Gly
1900

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: protein

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Xaa Leu Leu Cys Cys Pro Ser Trp Ser Thr Xaa Cys Asp His Glu Ala
1 5 10 15

Tyr Cys Cys Leu Thr Pro Arg Leu Lys Arg Ser Tyr His Leu Ser Leu
20 25 30

Gln Val Ala Gly
35

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1534 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GAGGCTAGAG GGCAGGCACT TTATGGCAAA CTCAGGTAGA ATTCTTCCTC TTCCGTCTCT 60

TTCCTTTTAC GTCATCGGGG AGACTGGGTG GCAATCGCAG CCCGAGAGAC GCATGGCTCT 120

TTCTGCCCTC CATCCTCTGA TGTACCTTGA TTTCGTATTC TGAGAGGCTG CTGCTTAGCG 180

GTAGCCCCTT GGTTTCCGTG GCAACGGAAA AGCGCGGGAA TTACAGATAA ATTAAAACTG 240

CGACTGCGCG GCGTGAGCTC GCTGAGACTT CCTGGACCCC GCACCAGGCT GTGGGGTTTC 300

TCAGATAACT GGGCCCCTGC GCTCAGGAGG CCTTCACCCT CTGCTCTGGG TAAAGGTAGT 360

AGAGTCCCGG GAAAGGGACA GGGGGCCCAA GTGATGCTCT GGGGTACTGG CGTGGGAGAG 420

TGGATTTCCG AAGCTGACAG ATGGGTATTC TTTGACGGGG GGTAGGGGCG GAACCTGAGA 480

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GGCGTAAGGC GTTGTGAACC CTGGGGAGGG GGGCAGTTTG TAGGTCGCGA GGGAAGCGCT     540
GAGGATCAGG AAGGGGGCAC TGAGTGTCCG TGGGGGAATC CTCGTGATAG GAACTGGAAT     600
ATGCCTTGAG GGGGACACTA TGTCTTTAAA AACGTCGGCT GGTCATGAGG TCAGGAGTTC     660
CAGACCAGCC TGACCAACGT GGTGAAACTC CGTCTCTACT AAAAATACNA AAATTAGCCG     720
GGCGTGGTGC CGCTCCAGCT ACTCAGGAGG CTGAGGCAGG AGAATCGCTA GAACCCGGGA     780
GGCGGAGGTT GCAGTGAGCC GAGATCGCGC CATTGCACTC CAGCCTGGGC GACAGAGCGA     840
GACTGTCTCA AAACAAAACA AAACAAAACA AAACAAAAAA CACCGGCTGG TATGTATGAG     900
AGGATGGGAC CTTGTGGAAG AAGAGGTGCC AGGAATATGT CTGGGAAGGG GAGGAGACAG     960
GATTTTGTGG GAGGGAGAAC TTAAGAACTG GATCCATTTG CGCCATTGAG AAAGCGCAAG    1020
AGGGAAGTAG AGGAGCGTCA GTAGTAACAG ATGCTGCCGG CAGGGATGTG CTTGAGGAGG    1080
ATCCAGAGAT GAGAGCAGGT CACTGGGAAA GGTTAGGGGC GGGGAGGCCT TGATTGGTGT    1140
TGGTTTGGTC GTTGTTGATT TTGGTTTTAT GCAAGAAAAA GAAAACAACC AGAAACATTG    1200
GAGAAAGCTA AGGCTACCAC CACCTACCCG GTCAGTCACT CCTCTGTAGC TTTCTCTTTC    1260
TTGGAGAAAG GAAAAGACCC AAGGGGTTGG CAGCGATATG TGAAAAAATT CAGAATTTAT    1320
GTTGTCTAAT TACAAAAAGC AACTTCTAGA ATCTTTAAAA ATAAAGGACG TTGTCATTAG    1380
TTCTTCTGGT TTGTATTATT CTAAAACCTT CCAAATCTTC AAATTTACTT TATTTTAAAA    1440
TGATAAAATG AAGTTGTCAT TTTATAAACC TTTTAAAAAG ATATATATAT ATGTTTTTCT    1500
AATGTGTTAA AGTTCATTGG AACAGAAAGA AATG                                1534
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(2) INFORMATION FOR SEQ ID NO:14:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1534 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear
- (i i) MOLECULE TYPE: DNA (genomic)
- (i i i) HYPOTHETICAL: NO
- (i v) ANTI-SENSE: NO
- (v i) ORIGINAL SOURCE:
  - (A) ORGANISM: Homo sapiens
- (x i) SEQUENCE DESCRIPTION: SEQ ID NO:14:

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GAGGCTAGAG GGCAGGCACT TTATGGCAAA CTCAGGTAGA ATTCTTCCTC TTCCGTCTCT      60
TTCCTTTTAC GTCATCGGGG AGACTGGGTG GCAATCGCAG CCCGAGAGAC GCATGGCTCT     120
TTCTGCCCTC CATCCTCTGA TGTACCTTGA TTTCGTATTC TGAGAGGCTG CTGCTTAGCG     180
GTAGCCCCTT GGTTTCCGTG GCAACGGAAA AGCGCGGGAA TTACAGATAA ATTAAAACTG     240
CGACTGCGCG GCGTGAGCTC GCTGAGACTT CCTGGACCCC GCACCAGGCT GTGGGGTTTC     300
TCAGATAACT GGGCCCCTGC GCTCAGGAGG CCTTCACCCT CTGCTCTGGG TAAAGGTAGT     360
AGAGTCCCGG GAAAGGGACA GGGGGCCCAA GTGATGCTCT GGGGTACTGG CGTGGGAGAG     420
TGGATTTCCG AAGCTGACAG ATGGGTATTC TTTGACGGGG GGTAGGGGCG GAACCTGAGA     480
GGCGTAAGGC GTTGTGAACC CTGGGGAGGG GGGCAGTTTG TAGGTCGCGA GGGAAGCGCT     540
GAGGATCAGG AAGGGGGCAC TGAGTGTCCG TGGGGGAATC CTCGTGATAG GAACTGGAAT     600
ATGCCTTGAG GGGGACACTA TGTCTTTAAA AACGTCGGCT GGTCATGAGG TCAGGAGTTC     660
CAGACCAGCC TGACCAACGT GGTGAAACTC CGTCTCTACT AAAAATACNA AAATTAGCCG     720
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GGCGTGGTGC CGCTCCAGCT ACTCAGGAGG CTGAGGCAGG AGAATCGCTA GAACCCGGGA 780

GGCGGAGGTT GCAGTGAGCC GAGATCGCGC CATTGCACTC CAGCCTGGGC GACAGAGCGA 840

GACTGTCTCA AAACAAAACA AAACAAAACA AAACAAAAAA CACCGGCTGG TATGTATGAG 900

AGGATGGGAC CTTGTGGAAG AAGAGGTGCC AGGAATATGT CTGGGAAGGG GAGGAGACAG 960

GATTTTGTGG GAGGGAGAAC TTAAGAACTG GATCCATTTG CGCCATTGAG AAAGCGCAAG 1020

AGGGAAGTAG AGGAGCGTCA GTAGTAACAG ATGCTGCCGG CAGGGATGTG CTTGAGGAGG 1080

ATCCAGAGAT GAGAGCAGGT CACTGGGAAA GGTTAGGGGC GGGGAGGCCT TGATTGGTGT 1140

TGGTTTGGTC GTTGTTGATT TTGGTTTTAT GCAAGAAAAA GAAAACAACC AGAAACATTG 1200

GAGAAAGCTA AGGCTACCAC CACCTACCCG GTCAGTCACT CCTCTGTAGC TTTCTCTTTC 1260

TTGGAGAAAG GAAAAGACCC AAGGGGTTGG CAGCGATATG TGAAAAAATT CAGAATTTAT 1320

GTTGTCTAAT TACAAAAAGC AACTTCTAGA ATCTTTAAAA ATAAAGGACG TTGTCATTAG 1380

TTCTTCTGGT TTGTATTATT CTAAAACCTT CCAAATCTTC AAATTTACTT TATTTTAAAA 1440

TGATAAAATG AAGTTGTCAT TTTATAAACC TTTTAAAAAG ATATATATAT ATGTTTTTCT 1500

AATGTGTTAA AGTTCATTGG AACAGAAAGA AATGGATTTA TCTGCTCTTC GCGTTGAAGA 1560

AGTACAAAAT GTCATTAATG CTATGCAGAA AATCTTAGAG TGTCCCATCT GGTAAGTCAG 1620

CACAAGAGTG TATTAATTTG GGATTCCTAT GATTATCTCC TATGCAAATG AACAGAATTG 1680

ACCTTACATA CTAGGGAAGA AAAGACATGT CTAGTAAGAT TAGGCTATTG TAATTGCTGA 1740

TTTTCTTAAC TGAAGAACTT TAAAAATATA GAAAATGATT CCTTGTTCTC CATCCACTCT 1800

GCCTCTCCCA CTCCTCTCCT TTTCAACACA ATCCTGTGGT CCGGGAAAGA CAGGGCTCTG 1860

TCTTGATTGG TTCTGCACTG GGCAGGATCT GTTAGATACT GCATTTGCTT TCTCCAGCTC 1920

TAAA 1924

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 631 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:15:

AAATGCTGAT GATAGTATAG AGTATTGAAG GGATCAATAT AATTCTGTTT TGATATCTGA 60

AAGCTCACTG AAGGTAAGGA TCGTATTCTC TGCTGTATTC TCAGTTCCTG ACACAGCAGA 120

CATTTAATAA ATATTGAACG AACTTGAGGC CTTATGTTGA CTCAGTCATA ACAGCTCAAA 180

GTTGAACTTA TTCACTAAGA ATAGCTTTAT TTTTAAATAA ATTATTGAGC CTCATTTATT 240

TTCTTTTTCT CCCCCCCCTA CCCTGCTAGT CTGGAGTTGA TCAAGGAACC TGTCTCCACA 300

AAGTGTGACC ACATATTTTG CAAGTAAGTT TGAATGTGTT ATGTGGCTCC ATTATTAGCT 360

TTTGTTTTTG TCCTTCATAA CCCAGGAAAC ACCTAACTTT ATAGAAGCTT TACTTTCTTC 420

AATTAAGTGA GAACGAAAAT CCAACTCCAT TTCATTCTTT CTCAGAGAGT ATATAGTTAT 480

CAAAAGTTGG TTGTAATCAT AGTTCCTGGT AAAGTTTTGA CATATATTAT CTTTTTTTTT 540

-continued

TTTTGAGACA AGTCTCGCTC TGTCGCCCAG GCTGGAGTGC AGTGGCATGA GGCTTGCTCA 600

CTGCACCTCC GCCCCCGAGT TCAGCGACTC T 631

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 481 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:16:

TGAGATCTAG ACCACATGGT CAAAGAGATA GAATGTGAGC AATAAATGAA CCTTAAATTT 60

TTCAACAGCT ACTTTTTTTT TTTTTTTTTG AGACAGGGKC TTACTCTGTT GTCCCAGCTG 120

GAGTACAGWG TGCGATCATG AGGCTTACTG TTGCTTGACT CCTAGGCTCA AGCGATCCTA 180

TCACCTCAGT CTCCAAGTAG CTGGACTGTA AGTGCACACC ACCATATCCA GCTAAATTTT 240

GTGTTTTCTG TAGAGACGGG GTTTCGCCAT GTTTCCCAGG CTGGTCTTGA ACTTTGGGCT 300

TAACCCGTCT GCCCACCTAG GCATCCCAAA GTGCTAGGAT TACAGGTGTG AGTCATCATG 360

CCTGGCCAGT ATTTTAGTTA GCTCTGTCTT TTCAAGTCAT ATACAAGTTC ATTTTCTTTT 420

AAGTTTAGTT AACAACCTTA TATCATGTAT TCTTTTCTAG CATAAAGAAA GATTCGAGGC 480

C 481

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 522 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:17:

TGTGATCATA ACAGTAAGCC ATATGCATGT AAGTTCAGTT TTCATAGATC ATTGCTTATG 60

TAGTTTAGGT TTTTGCTTAT GCAGCATCCA AAAACAATTA GGAAACTATT GCTTGTAATT 120

CACCTGCCAT TACTTTTTAA ATGGCTCTTA AGGGCAGTTG TGAGATTATC TTTTCATGGC 180

TATTTGCCTT TTGAGTATTC TTTCTACAAA AGGAAGTAAA TTAAATTGTT CTTTCTTTCT 240

TTATAATTTA TAGATTTTGC ATGCTGAAAC TTCTCAACCA GAAGAAAGGG CCTTCACAGT 300

GTCCTTTATG TAAGAATGAT ATAACCAAAA GGTATATAAT TTGWTAATGA TGCTAGGTTG 360

GAAGCAACCA CAGTAGGAAA AAGTAGAAAT TATTTAATAA CATAGCGTTC CTATAAAACC 420

ATTCATCAGA AAAATTTATA AAAGAGTTTT TAGCACACAG TAAATTATTT CCAAAGTTAT 480

TTTCCTGAAA GTTTTATGGG CATCTGCCTT ATACAGGTAT TG 522

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(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 465 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```
GGTAGGCTTA AATGAATGAC AAAAAGTTAC TAAATCACTG CCATCACACG GTTTATACAG    60
ATGTCAATGA TGTATTGATT ATAGAGGTTT TCTACTGTTG CTGCATCTTA TTTTTATTTG   120
TTTACATGTC TTTTCTTATT TTAGTGTCCT TAAAAGGTTG ATAATCACTT GCTGAGTGTG   180
TTTCTCAAAC AATTTAATTT CAGGAGCCTA CAAGAAACTA CGAGATTTAG TCAACTTGTT   240
GAAGAGCTAT TGAAAATCAT TTGTGCTTTT CAGCTTGACA CAGGTTTGGA GTGTAAGTGT   300
TGAATATCCC AAGAATGACA CTCAAGTGCT GTCCATGAAA ACTCAGGAAG TTTGCACAAT   360
TACTTTCTAT GACGTGGTGA TAAGACCTTT TAGTCTAGGT TAATTTTAGT TCTGTATCTG   420
TAATCTATTT TAAAAAATTA CTCCCACTGG TCTCACACCT TATTT                   465
```

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 513 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```
AAAAAATCAC AGGTAACCTT AATGCATTGT CTTAACACAA CAAAGAGCAT ACATAGGGTT    60
TCTCTTGGTT TCTTTGATTA TAATTCATAC ATTTTTCTCT AACTGCAAAC ATAATGTTTT   120
CCCTTGTATT TTACAGATGC AAACAGCTAT AATTTTGCAA AAAAGGAAAA TAACTCTCCT   180
GAACATCTAA AAGATGAAGT TTCTATCATC CAAAGTATGG GCTACAGAAA CCGTGCCAAA   240
AGACTTCTAC AGAGTGAACC CGAAAATCCT TCCTTGGTAA AACCATTTGT TTTCTTCTTC   300
TTCTTCTTCT TCTTTTCTTT TTTTTTTCTT TTTTTTTTTG AGATGGAGTC TTGCTCTGTG   360
GCCCAGGCTA GAAGCAGTCC TCCTGCCTTA GCCNCCTTAG TAGCTGGGAT TACAGGCACG   420
CGCACCATGC CAGGCTAATT TTTGTATTTT TAGTAGAGAC GGGGTTTCAT CATGTTGGCC   480
AGGCTGGTCT CGAACTCCTA ACCTCAGGTG ATC                                513
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(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6789 base pairs
(B) TYPE: nucleic acid

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(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:20:

ATGATGGAGA TCTTAAAAAG TAATCATTCT GGGGCTGGGC GTAGTAGCTT GCACCTGTAA 60

TCCCAGCACT TCGGGAGGCT GAGGCAGGCA GATAATTTGA GGTCAGGAGT TTGAGACCAG 120

CCTGGCCAAC ATGGTGAAAC CCATCTCTAC TAAAAATACA AAAATTAGCT GGGTGTGGTG 180

GCACGTACCT GTAATCCCAG CTACTCGGGA GGCGGAGGCA CAAGAATTGC TTGAACCTAG 240

GACGCGGAGG TTGCAGCGAG CCAAGATCGC GCCACTGCAC TCCAGCCTGG GCCGTAGAGT 300

GAGACTCTGT CTCAAAAAAG AAAAAAAAGT AATTGTTCTA GCTGGGCGCA GTGGCTCTTG 360

CCTGTAATCC CAGCACTTTG GGAGGCCAAG GCGGGTGGAT CTCGAGTCCT AGAGTTCAAG 420

ACCAGCCTAG GCAATGTGGT GAAACCCCAT CGCTACAAAA AATACAAAAA TTAGCCAGGC 480

ATGGTGGCGT GCGCATGTAG TCCCAGCTCC TTGGGAGGCT GAGGTGGGAG GATCACTTGA 540

ACCCAGGAGA CAGAGGTTGC AGTGAACCGA GATCACGCCA CCACGCTCCA GCCTGGGCAA 600

CAGAACAAGA CTCTGTCTAA AAAAATACAA ATAAAATAAA AGTAGTTCTC ACAGTACCAG 660

CATTCATTTT TCAAAAGATA TAGAGCTAAA AAGGAAGGAA AAAAAAAGTA ATGTTGGGCT 720

TTTAAATACT CGTTCCTATA CTAAATGTTC TTAGGAGTGC TGGGGTTTTA TTGTCATCAT 780

TTATCCTTTT TAAAAATGTT ATTGGCCAGG CACGGTGGCT CATGGCTGTA ATCCCAGCAC 840

TTTGGGAGGC CGAGGCAGGC AGATCACCTG AGGTCAGGAG TGTGAGACCA GCCTGGCCAA 900

CATGGCGAAA CCTGTCTCTA CTAAAAATAC AAAAATTAAC TAGGCGTGGT GGTGTACGCC 960

TGTAGTCCCA GCTACTCGGG AGGCTGAGGC AGGAGAATCA ACTGAACCAG GGAGGTGGAG 1020

GTTGCAGTGT GCCGAGATCA CGCCACTGCA CTCTAGCCTG GCAACAGAGC AAGATTCTGT 1080

CTCAAAAAAA AAAAACATAT ATACACATAT ATCCCAAAGT GCTGGGATTA CATATATATA 1140

TATATATATA TATTATATAT ATATATATAT ATATATGTGA TATATATGTG ATATATATAT 1200

AACATATATA TATGTAATAT ATATGTGATA TATATATAAT ATATATATGT AATATATATG 1260

TGATATATAT ATATACACAC ACACACACAT ATATATGTAT GTGTGTGTAC ACACACACAC 1320

ACAAATTAGC CAGGCATAGT TGCACACGCT TGGTAGACCC AGCTACTCAG GAGGCTGAGG 1380

GAGGAGAATC TCTTGAACTT AGGAGGCGGA GGTTGCAGTG AGCTGAGATT GCGCCACTGC 1440

ACTCCAGCCT GGGTGACAGA GCAGGACTCT GTACACCCCC CAAAACAAAA AAAAAAGTTA 1500

TCAGATGTGA TTGGAATGTA TATCAAGTAT CAGCTTCAAA ATATGCTATA TTAATACTTC 1560

AAAAATTACA CAAATAATAC ATAATCAGGT TTGAAAAATT TAAGACAACM SAARAAAAAA 1620

WYCMAATCAC AMATATCCCA CACATTTTAT TATTMCTMCT MCWATTATTT TGWAGAGMCT 1680

GGGTCTCACY CYKTTGCTWA TGCTGGTCTT TGAACYCCYK GCCYCAARCA RTCCTSCTCC 1740

ARCCTCCCAA RGTGCTGGGG ATWATAGGCA TGARCTAACC GCACCCAGCC CCAGACATTT 1800

TAGTGTGTAA ATTCCTGGGC ATTTTTTCAA GGCATCATAC ATGTTAGCTG ACTGATGATG 1860

GTCAATTTAT TTTGTCCATG GTGTCAAGTT TCTCTTCAGG AGGAAAAGCA CAGAACTGGC 1920

CAACAATTGC TTGACTGTTC TTTACCATAC TGTTTAGCAG GAAACCAGTC TCAGTGTCCA 1980

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ACTCTCTAAC CTTGGAACTG TGAGAACTCT GAGGACAAAG CAGCGGATAC AACCTCAAAA   2040

GACGTCTGTC TACATTGAAT TGGGTAAGGG TCTCAGGTTT TTTAAGTATT TAATAATAAT   2100

TGCTGGATTC CTTATCTTAT AGTTTTGCCA AAAATCTTGG TCATAATTTG TATTTGTGGT   2160

AGGCAGCTTT GGGAAGTGAA TTTTATGAGC CCTATGGTGA GTTATAAAAA ATGTAAAAGA   2220

CGCAGTTCCC ACCTTGAAGA ATCTTACTTT AAAAAGGGAG CAAAAGAGGC CAGGCATGGT   2280

GGCTCACACC TGTAATCCCA GCACTTTGGG AGGCCAAAGT GGGTGGATCA CCTGAGGTCG   2340

GGAGTTCGAG ACCAGCCTAG CCAACATGGA GAAACTCTGT CTGTACCAAA AAATAAAAAA   2400

TTAGCCAGGT GTGGTGGCAC ATAACTGTAA TCCCAGCTAC TCGGGAGGCT GAGGCAGGAG   2460

AATCACTTGA ACCCGGGAGG TGGAGGTTGC GGTGAACCGA GATCGCACCA TTGCACTCCA   2520

GCCTGGGCAA AAATAGCGAA ACTCCATCTA AAAAAAAAAA AGAGAGCAAA AGAAAGAMTM   2580

TCTGGTTTTA AMTMTGTGTA AATATGTTTT TGGAAAGATG GAGAGTAGCA ATAAGAAAAA   2640

ACATGATGGA TTGCTACAGT ATTTAGTTCC AAGATAAATT GTACTAGATG AGGAAGCCTT   2700

TTAAGAAGAG CTGAATTGCC AGGCGCAGTG GCTCACGCCT GTAATCCCAG CACTTTGGGA   2760

GGCCGAGGTG GGCGGATCAC CTGAGGTCGG GAGTTCAAGA CCAGCCTGAC CAACATGGAG   2820

AAACCCCATC TCTACTAAAA AAAAAAAAAA AAAAATTAGC CGGGGTGGTG GCTTATGCCT   2880

GTAATCCCAG CTACTCAGGA GGCTGAGGCA GGAGAATCGC TTGAACCCAG GAAGCAGAGG   2940

TTGCAGTGAG CCAAGATCGC ACCATTGCAC TCCAGCCTAG GCAACAAGAG TGAAACTCCA   3000

TCTCAAAAAA AAAAAAAAAG AGCTGAATCT TGGCTGGGCA GGATGGCTCG TGCCTGTAAT   3060

CCTAACGCTT TGGAAGACCG AGGCAGAAGG ATTGGTTGAG TCCACGAGTT TAAGACCAGC   3120

CTGGCCAACA TAGGGGAACC CTGTCTCTAT TTTTAAAATA ATAATACATT TTTGGCCGGT   3180

GCGGTGGCTC ATGCCTGTAA TCCCAATACT TTGGGAGGCT GAGGCAGGTA GATCACCTGA   3240

GGTCAGAGTT CGAGACCAGC CTGGATAACC TGGTGAAACC CCTCTTTACT AAAAATACAA   3300

AAAAAAAAAA AAATTAGCTG GGTGTGGTAG CACATGCTTG TAATCCCAGC TACTTGGGAG   3360

GCTGAGGCAG GAGAATCGCT TGAACCAGGG AGGCGGAGGT TACAATGAGC CAACACTACA   3420

CCACTGCACT CCAGCCTGGG CAATAGAGTG AGACTGCATC TCAAAAAAAT AATAATTTTT   3480

AAAAATAATA AATTTTTTTA AGCTTATAAA AAGAAAAGTT GAGGCCAGCA TAGTAGCTCA   3540

CATCTGTAAT CTCAGCAGTG GCAGAGGATT GCTTGAAGCC AGGAGTTTGA GACCAGCCTG   3600

GGCAACATAG CAAGACCTCA TCTCTACAAA AAAATTTCTT TTTTAAATTA GCTGGGTGTG   3660

GTGGTGTGCA TCTGTAGTCC CAGCTACTCA GGAGGCAGAG GTGAGTGGAT ACATTGAACC   3720

CAGGAGTTTG AGGCTGTAGT GAGCTATGAT CATGCCACTG CACTCCAACC TGGGTGACAG   3780

AGCAAGACCT CCAAAAAAAA AAAAAAAAGA GCTGCTGAGC TCAGAATTCA AACTGGGCTC   3840

TCAAATTGGA TTTTCTTTTA GAATATATTT ATAATTAAAA AGGATAGCCA TCTTTTGAGC   3900

TCCCAGGCAC CACCATCTAT TTATCATAAC ACTTACTGTT TTCCCCCCTT ATGATCATAA   3960

ATTCCTAGAC AACAGGCATT GTAAAAATAG TTATAGTAGT TGATATTTAG GAGCACTTAA   4020

CTATATTCCA GGCACTATTG TGCTTTTCTT GTATAACTCA TTAGATGCTT GTCAGACCTC   4080

TGAGATTGTT CCTATTATAC TTATTTTACA GATGAGAAAA TTAAGGCACA GAGAAGTTAT   4140

GAAATTTTTC CAAGGTATTA AACCTAGTAA GTGGCTGAGC CATGATTCAA ACCTAGGAAG   4200

TTAGATGTCA GAGCCTGTGC TTTTTTTTTG TTTTTGTTTT TGTTTTCAGT AGAAACGGGG   4260

GTCTCACTTT GTTGGCCAGG CTGGTCTTGA ACTCCTAACC TCAAATAATC CACCCATCTC   4320

GGCCTCCTCA AGTGCTGGGA TTACAGGTGA GAGCCACTGT GCCTGGCGAA GCCCATGCCT   4380
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TTAACCACTT CTCTGTATTA CATACTAGCT TAACTAGCAT TGTACCTGCC ACAGTAGATG   4440
CTCAGTAAAT ATTTCTAGTT GAATATCTGT TTTTCAACAA GTACATTTTT TTAACCCTTT   4500
TAATTAAGAA AACTTTTATT GATTTATTTT TTGGGGGGAA ATTTTTTAGG ATCTGATTCT   4560
TCTGAAGATA CCGTTAATAA GGCAACTTAT TGCAGGTGAG TCAAAGAGAA CCTTTGTCTA   4620
TGAAGCTGGT ATTTTCCTAT TTAGTTAATA TTAAGGATTG ATGTTTCTCT CTTTTTAAAA   4680
ATATTTTAAC TTTTATTTTA GGTTCAGGGA TGTATGTGCA GTTTGTTATA TAGGTAAACA   4740
CACGACTTGG GATTTGGTGT ATAGATTTTT TTCATCATCC GGGTACTAAG CATACCCCAC   4800
AGTTTTTTGT TTGCTTTCTT TCTGAATTTC TCCCTCTTCC CACCTTCCTC CCTCAAGTAG   4860
GCTGGTGTTT CTCCAGACTA GAATCATGGT ATTGGAAGAA ACCTTAGAGA TCATCTAGTT   4920
TAGTTCTCTC ATTTTATAGT GGAGGAAATA CCCTTTTTGT TTGTTGGATT TAGTTATTAG   4980
CACTGTCCAA AGGAATTTAG GATAACAGTA GAACTCTGCA CATGCTTGCT TCTAGCAGAT   5040
TGTTCTCTAA GTTCCTCATA TACAGTAATA TTGACACAGC AGTAATTGTG ACTGATGAAA   5100
ATGTTCAAGG ACTTCATTTT CAACTCTTTC TTTCCTCTGT TCCTTATTTC CACATATCTC   5160
TCAAGCTTTG TCTGTATGTT ATATAATAAA CTACAAGCAA CCCCAACTAT GTTACCTACC   5220
TTCCTTAGGA ATTATTGCTT GACCCAGGTT TTTTTTTTTT TTTTTTTGGA GACGGGGTCT   5280
TGCCCTGTTG CCAGGATGGA GTGTAGTGGC GCCATCTCGG CTCACTGCAA TCTCCAACTC   5340
CCTGGTTCAA GCGATTCTCC TGTCTCAATC TCACGAGTAG CTGGGACTAC AGGTATACAC   5400
CACCACGCCC GGTTAATTGA CCATTCCATT TCTTTCTTTC TCTCTTTTTT TTTTTTTTTT   5460
TTGAGACAGA GTCTTGCTCT GTTGCCCAGG CTGGAGTACA GAGGTGTGAT CTCACCTCTC   5520
CGCAACGTCT GCCTCCCAGG TTGAAGCCAT ACTCCTGCCT CAGCCTCTCT AGTAGCTGGG   5580
ACTACAGGCG CGCGCCACCA CACCCGGCTA ATTTTTGTAT TTTTAGTAGA GATGGGGTTT   5640
CACCATGTTG GCCAGGCTGG TCTTGAACTC ATGACCTCAA GTGGTCCACC CGCCTCAGCC   5700
TCCCAAAGTG CTGGAATTAC AGGCTTGAGC CACCGTGCCC AGCAACCATT TCATTTCAAC   5760
TAGAAGTTTC TAAAGGAGAG AGCAGCTTTC ACTAACTAAA TAAGATTGGT CAGCTTTCTG   5820
TAATCGAAAG AGCTAAAATG TTTGATCTTG GTCATTTGAC AGTTCTGCAT ACATGTAACT   5880
AGTGTTTCTT ATTAGGACTC TGTCTTTTCC CTATAGTGTG GGAGATCAAG AATTGTTACA   5940
AATCACCCCT CAAGGAACCA GGGATGAAAT CAGTTTGGAT TCTGCAAAAA AGGGTAATGG   6000
CAAAGTTTGC CAACTTAACA GGCACTGAAA AGAGAGTGGG TAGATACAGT ACTGTAATTA   6060
GATTATTCTG AAGACCATTT GGGACCTTTA CAACCCACAA AATCTCTTGG CAGAGTTAGA   6120
GTATCATTCT CTGTCAAATG TCGTGGTATG GTCTGATAGA TTTAAATGGT ACTAGACTAA   6180
TGTACCTATA ATAAGACCTT CTTGTAACTG ATTGTTGCCC TTTCGCTTTT TTTTTTGTTT   6240
GTTTGTTTGT TTTTTTTTGA GATGGGGTCT CACTCTGTTG CCCAGGCTGG AGTGCAGTGA   6300
TGCAATCTTG GCTCACTGCA ACCTCCACCT CCAAAGGCTC AAGCTATCCT CCCACTTCAG   6360
CCTCCTGAGT AGCTGGGACT ACAGGCGCAT GCCACCACAC CCGGTTAATT TTTTGTGGTT   6420
TTATAGAGAT GGGGTTTCAC CATGTTACCG AGGCTGGTCT CAAACTCCTG GACTCAAGCA   6480
GTCTGCCCAC TTCAGCCTCC CAAAGTGCTG CAGTTACAGG CTTGAGCCAC TGTGCCTGGC   6540
CTGCCCTTTA CTTTTAATTG GTGTATTTGT GTTTCATCTT TTACCTACTG GTTTTTAAAT   6600
ATAGGGAGTG GTAAGTCTGT AGATAGAACA GAGTATTAAG TAGACTTAAT GGCCAGTAAT   6660
CTTTAGAGTA CATCAGAACC AGTTTTCTGA TGGCCAATCT GCTTTTAATT CACTCTTAGA   6720
CGTTAGAGAA ATAGGTGTGG TTTCTGCATA GGGAAAATTC TGAAATTAA              6769
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(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4249 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:21:

GATCCTAAGT GGAAATAATC TAGGTAAATA GGAATTAAAT GAAAGAGTAT GAGCTACATC 60

TTCAGTATAC TTGGTAGTTT ATGAGGTTAG TTTCTCTAAT ATAGCCAGTT GGTTGATTTC 120

CACCTCCAAG GTGTATGAAG TATGTATTTT TTTAATGACA ATTCAGTTTT TGAGTACCTT 180

GTTATTTTTG TATATTTTCA GCTGCTTGTG AATTTTCTGA GACGGATGTA ACAAATACTG 240

AACATCATCA ACCCAGTAAT AATGATTTGA ACACCACTGA GAAGCGTGCA GCTGAGAGGC 300

ATCCAGAAAA GTATCAGGGT AGTTCTGTTT CAAACTTGCA TGTGGAGCCA TGTGGCACAA 360

ATACTCATGC CAGCTCATTA CAGCATGAGA ACAGCAGTTT ATTACTCACT AAAGACAGAA 420

TGAATGTAGA AAAGGCTGAA TTCTGTAATA AAAGCAAACA GCCTGGCTTA GCAAGGAGCC 480

AACATAACAG ATGGGCTGGA AGTAAGGAAA CATGTAATGA TAGGCGGACT CCCAGCACAG 540

AAAAAAAGGT AGATCTGAAT GCTGATCCCC TGTGTGAGAG AAAAGAATGG AATAAGCAGA 600

AACTGCCATG CTCAGAGAAT CCTAGAGATA CTGAAGATGT TCCTTGGATA ACACTAAATA 660

GCAGCATTCA GAAAGTTAAT GAGTGGTTTT CCAGAAGTGA TGAACTGTTA GGTTCTGATG 720

ACTCACATGA TGGGGAGTCT GAATCAAATG CCAAAGTAGC TGATGTATTG GACGTTCTAA 780

ATGAGGTAGA TGAATATTCT GGTTCTTCAG AGAAAATAGA CTTACTGGCC AGTGATCCTC 840

ATGAGGCTTT AATATGTAAA AGTGAAAGAG TTCACTCCAA ATCAGTAGAG AGTAATATTG 900

AAGGCCAAAT ATTTGGGAAA ACCTATCGGA AGAAGGCAAG CCTCCCCAAC TTAAGCCATG 960

TAACTGAAAA TCTAATTATA GGAGCATTTG TTACTGAGCC ACAGATAATA CAAGAGCGTC 1020

CCCTCACAAA TAAATTAAAG CGTAAAAGGA GACCTACATC AGGCCTTCAT CCTGAGGATT 1080

TTATCAAGAA AGCAGATTTG GCAGTTCAAA AGACTCCTGA AATGATAAAT CAGGGAACTA 1140

ACCAAACGGA GCAGAATGGT CAAGTGATGA ATATTACTAA TAGTGGTCAT GAGAATAAAA 1200

CAAAAGGTGA TTCTATTCAG AATGAGAAAA ATCCTAACCC AATAGAATCA CTCGAAAAAG 1260

AATCTGCTTT CAAAACGAAA GCTGAACCTA TAAGCAGCAG TATAAGCAAT ATGGAACTCG 1320

AATTAAATAT CCACAATTCA AAAGCACCTA AAAAGAATAG GCTGAGGAGG AAGTCTTCTA 1380

CCAGGCATAT TCATGCGCTT GAACTAGTAG TCAGTAGAAA TCTAAGCCCA CCTAATTGTA 1440

CTGAATTGCA AATTGATAGT TGTTCTAGCA GTGAAGAGAT AAAGAAAAAA AAGTACAACC 1500

AAATGCCAGT CAGGCACAGC AGAAACCTAC AACTCATGGA AGGTAAAGAA CCTGCAACTG 1560

GAGCCAAGAA GAGTAACAAG CCAAATGAAC AGACAAGTAA AAGACATGAC AGCGATACTT 1620

TCCCAGAGCT GAAGTTAACA AATGCACCTG GTTCTTTTAC TAAGTGTTCA AATACCAGTG 1680

AACTTAAAGA ATTTGTCAAT CCTAGCCTTC CAAGAGAAGA AAAAGAAGAG AACTAGAAAC 1740

AGTTAAAGTG TCTAATAATG CTGAAGACCC CAAAGATCTC ATGTTAAGTG GAGAAAGGGT 1800

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TTTGCAAACT GAAAGATCTG TAGAGAGTAG CAGTATTTCA TTGGTACCTG GTACTGATTA   1860

TGGCACTCAG GAAAGTATCT CGTTACTGGA AGTTAGCACT CTAGGCAAGG CAAAAACAGA   1920

ACCAAATAAA TGTGTGAGTC AGTGTGCAGC ATTTGAAAAC CCCAAGGGAC TAATTCATGG   1980

TTGTTCCAAA GATAATAGAA ATGACACAGA AGGCTTTAAG TATCCATTGG GACATGAAGT   2040

TAACCACAGT CGGGAAACAA GCATAGAAAT GGAAGAAAGT GAACTTGATG CTCAGTATTT   2100

GCAGAATACA TTCAAGGTTT CAAAGCGCCA GTCATTTGCT CCGTTTTCAA ATCCAGGAAA   2160

TGCAGAAGAG GAATGTGCAA CATTCTCTGC CCACTCTGGG TCCTTAAAGA AACAAAGTCC   2220

AAAAGTCACT TTTGAATGTG AACAAAAGGA AGAAAATCAA GGAAAGAATG AGTCTAATAT   2280

CAAGCCTGTA CAGACAGTTA ATATCACTGC AGGCTTTCCT GTGGTTGGTC AGAAAGATAA   2340

GCCAGTTGAT AATGCCAAAT GTAGTATCAA AGGAGGCTCT AGGTTTTGTC TATCATCTCA   2400

GTTCAGAGGC AACGAAACTG GACTCATTAC TCCAAATAAA CATGGACTTT TACAAAACCC   2460

ATATCGTATA CCACCACTTT TTCCCATCAA GTCATTTGTT AAAACTAAAT GTAAGAAAAA   2520

TCTGCTAGAG GAAAACTTTG AGGAACATTC AATGTCACCT GAAAGAGAAA TGGGAAATGA   2580

GAACATTCCA AGTACAGTGA GCACAATTAG CCGTAATAAC ATTAGAGAAA ATGTTTTTAA   2640

AGAAGCCAGC TCAAGCAATA TTAATGAAGT AGGTTCCAGT ACTAATGAAG TGGGCTCCAG   2700

TATTAATGAA ATAGGTTCCA GTGATGAAAA CATTCAAGCA GAACTAGGTA GAAACAGAGG   2760

GCCAAAATTG AATGCTATGC TTAGATTAGG GGTTTTGCAA CCTGAGGTCT ATAAACAAAG   2820

TCTTCCTGGA AGTAATTGTA AGCATCCTGA AATAAAAAAG CAAGAATATG AAGAAGTAGT   2880

TCAGACTGTT AATACAGATT TCTCTCCATA TCTGATTTCA GATAACTTAG AACAGCCTAT   2940

GGGAAGTAGT CATGCATCTC AGGTTTGTTC TGAGACACCT GATGACCTGT TAGATGATGG   3000

TGAAATAAAG GAAGATACTA GTTTTGCTGA AAATGACATT AAGGAAAGTT CTGCTGTTTT   3060

TAGCAAAAGC GTCCAGAAAG GAGAGCTTAG CAGGAGTCCT AGCCCTTTCA CCCATACACA   3120

TTTGGCTCAG GGTTACCGAA GAGGGGCCAA GAAATTAGAG TCCTCAGAAG AGAACTTATC   3180

TAGTGAGGAT GAAGAGCTTC CCTGCTTCCA ACACTTGTTA TTTGGTAAAG TAAACAATAT   3240

ACCTTCTCAG TCTACTAGGC ATAGCACCGT TGCTACCGAG TGTCTGTCTA AGAACACAGA   3300

GGAGAATTTA TTATCATTGA AGAATAGCTT AAATGACTGC AGTAACCAGG TAATATTGGC   3360

AAAGGCATCT CAGGAACATC ACCTTAGTGA GGAAACAAAA TGTTCTGCTA GCTTGTTTTC   3420

TTCACAGTGC AGTGAATTGG AAGACTTGAC TGCAAATACA AACACCCAGG ATCCTTTCTT   3480

GATTGGTTCT TCCAAACAAA TGAGGCATCA GTCTGAAAGC CAGGGAGTTG GTCTGAGTGA   3540

CAAGGAATTG GTTTCAGATG ATGAAGAAAG AGGAACGGGC TTGGAAGAAA ATAATCAAGA   3600

AGAGCAAAGC ATGGATTCAA ACTTAGGTAT TGGAACCAGG TTTTTGTGTT TGCCCCAGTC   3660

TATTTATAGA AGTGAGCTAA ATGTTTATGC TTTTGGGGAG CACATTTTAC AAATTTCCAA   3720

GTATAGTTAA AGGAACTGCT TCTTAAACTT GAAACATGTT CCTCCTAAGG TGCTTTTCAT   3780

AGAAAAAAGT CCTTCACACA GCTAGGACGT CATCTTTGAC TGAATGAGCT TTAACATCCT   3840

AATTACTGGT GGACTTACTT CTGGTTTCAT TTTATAAAGC AAATCCCGGT GTCCCAAAGC   3900

AAGGAATTTA ATCATTTTGT GTGACATGAA AGTAAATCCA GTCCTGCCAA TGAGAAGAAA   3960

AAGACACAGC AAGTTGCAGC GTTTATAGTC TGCTTTTACA TCTGAACCTC TGTTTTTGTT   4020

ATTTAAGGTG AAGCAGCATC TGGGTGTGAG AGTGAAACAA GCGTCTCTGA AGACTGCTCA   4080

GGGCTATCCT CTCAGAGTGA CATTTTAACC ACTCAGGTAA AAAGCGTGTG TGTGTGTGCA   4140

CATGCGTGTG TGTGGTGTCC TTTGCATTCA GTAGTATGTA TCCCACATTC TTAGGTTTGC   4200
```

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TGACATCATC TCTTTGAATT AATGGCACAA TTGTTTGTGG TTCATTGTC 4249

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 710 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:22:

NGNGAATGTA ATCCTAATAT TTCNCNCCNA CTTAAAAGAA TACCACTCCA ANGGCATCNC 60

AATACATCAA TCAATTGGGG AATTGGGATT TTCCCTCNCT AACATCANTG GAATAATTTC 120

ATGGCATTAA TTGCATGAAT GTGGTTAGAT TAAAAGGTGT TCATGCTAGA ACTTGTAGTT 180

CCATACTAGG TGATTTCAAT TCCTGTGCTA AAATTAATTT GTATGATATA TTNTCATTTA 240

ATGGAAAGCT TCTCAAAGTA TTTCATTTTC TTGGTACCAT TTATCGTTTT TGAAGCAGAG 300

GGATACCATG CAACATAACC TGATAAAGCT CCAGCAGGAA ATGGCTGAAC TAGAAGCTGT 360

GTTAGAACAG CATGGGAGCC AGCCTTCTAA CAGCTACCCT TCCATCATAA GTGACTCTTC 420

TGCCCTTGAG GACCTGCGAA ATCCAGAACA AAGCACATCA GAAAAAGGTG TGTATTGTTG 480

GCCAAACACT GATATCTTAA GCAAAATTCT TTCCTTCCCC TTTATCTCCT TCTGAAGAGT 540

AAGGACCTAG CTCCAACATT TTATGATCCT TGCTCAGCAC ATGGGTAATT ATGGAGCCTT 600

GGTTCTTGTC CCTGCTCACA ACTAATATAC CAGTCAGAGG GACCCAAGGC AGTCATTCAT 660

GTTGTCATCT GAGATACCTA CAACAAGTAG ATGCTATGGG GAGCCCATGG 710

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 473 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:23:

CCATTGGTGC TAGCATCTGT CTGTTGCATT GCTTGTGTTT ATAAAATTCT GCCTGATATA 60

CTTGTTAAAA ACCAATTTGT GTATCATAGA TTGATGCTTT TGAAAAAAAT CAGTATTCTA 120

ACCTGAATTA TCACTATCAG AACAAAGCAG TAAAGTAGAT TTGTTTTCTC ATTCCATTTA 180

AAGCAGTATT AACTTCACAG AAAAGTAGTG AATACCCTAT AAGCCAGAAT CCAGAAGGCC 240

TTTCTGCTGA CAAGTTTGAG GTGTCTGCAG ATAGTTCTAC CAGTAAAAAT AAAGAACCAG 300

GAGTGGAAAG GTAAGAAACA TCAATGTAAA GATGCTGTGG TATCTGACAT CTTTATTTAT 360

ATTGAACTCT GATTGTTAAT TTTTTTCACC ATACTTTCTC CAGTTTTTTT GCATACAGGC 420

-continued

```
ATTTATACAC TTTTATTGCT CTAGGATACT TCTTTTGTTT AATCCTATAT AGG            473
```

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 421 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```
GGATAAGNTC AAGAGATATT TTGATAGGTG ATGCAGTGAT NAATTGNGAA AATTTNCTGC      60
CTGCTTTTAA TCTTCCCCCG TTCTTTCTTC CTNCCTCCCT CCCTTCCTNC CTCCCGTCCT     120
TNCCTTTCCT TTCCCTCCCT TCCNCCTTCT TTCCNTCTNT CTTTCCTTTC TTTCCTGTCT     180
ACCTTTCTTT CCTTCCTCCC TTCCTTTTCT TTTCTTTCTT TCCTTTCCTT TTCTTTCCTT     240
TCTTTCCTTT CCTTTCTTTC TTGACAGAGT CTTGCTCTGT CACTCAGGCT GGAGTGCAGT     300
GGCGTGATCT CGNCTCACTG CAACCTCTGT CTCCCAGGTT CAAGCAATTT TCCTGCCTCA     360
GCCTCCCGAG TAGCTGAGAT TACAGGCGCC AGCCACCACA CCCAGCTACT GACCTGCTTT     420
T                                                                     421
```

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 997 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```
AAACAGCTGG GAGATATGGT GCCTCAGACC AACCCCATGT TATATGTCAA CCCTGACATA      60
TTGGCAGGCA ACATGAATCC AGACTTCTAG GCTGTCATGC GGGCTCTTTT TTGCCAGTCA     120
TTTCTGATCT CTCTGACATG AGCTGTTTCA TTTATGCTTT GGCTGCCCAG CAAGTATGAT     180
TTGTCCTTTC ACAATTGGTG GCGATGGTTT TCTCCTTCCA TTTATCTTTC TAGGTCATCC     240
CCTTCTAAAT GCCCATCATT AGATGATAGG TGGTACATGC ACAGTTGCTC TGGGAGTCTT     300
CAGAATAGAA ACTACCCATC TCAAGAGGAG CTCATTAAGG TTGTTGATGT GGAGGAGCAA     360
CAGCTGGAAG AGTCTGGGCC ACACGATTTG ACGGAAACAT CTTACTTGCC AAGGCAAGAT     420
CTAGGTAATA TTTCATCTGC TGTATTGGAA CAAACACTTT GATTTTACTC TGAATCCTAC     480
ATAAAGATAT TCTGGTTAAC CAACTTTTAG ATGTACTAGT CTATCATGGA CACTTTTGTT     540
ATACTTAATT AAGCCCACTT TAGAAAAATA GCTCAAGTGT TAATCAAGGT TTACTTGAAA     600
ATTATTGAAA CTGTTAATCC ATCTATATTT TAATTAATGG TTTAACTAAT GATTTTGAGG     660
```

-continued

ATGWGGGAGT CKTGGTGTAC TCTAMATGTA TTATTTCAGG CCAGGCATAG TGGCTCACGC 720

CTGGTAATCC CAGTAYTCMR GAGCCCGAGG CAGGTGGAGC CAGCTGAGGT CAGGAG[illegible]TCA 780

AGACCTGTCT TGGCCAACAT GGGNGAAACC CTGTCTTCTT CTTAAAAAAN ACAAAAAAAA 840

TTAACTGGGT TGTGCTTAGG TGNATGCCCC GNATCCTAGT TNTTCTTGNG GGTTGAGGGA 900

GGAGATCACN TTGGACCCCG GAGGGGNGGG TGGGGGNGAG CAGGNCAAAA CACNGACCCA 960

GCTGGGGTGG AAGGGAAGCC CACTCNAAAA AANNTTN 997

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 639 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:26:

TTTTTAGGAA ACAAGCTACT TTGGATTTCC ACCAACACCT GTATTCATGT ACCCATTTTT 60

CTCTTAACCT AACTTTATTG GTCTTTTTAA TTCTTAACAG AGACCAGAAC TTTGTAATTC 120

AACATTCATC GTTGTGTAAA TTAAACTTCT CCCATTCCTT TCAGAGGGAA CCCCTTACCT 180

GGAATCTGGA ATCAGCCTCT TCTCTGATGA CCCTGAATCT GATCCTTCTG AAGACAGAGC 240

CCCAGAGTCA GCTCGTGTTG GCAACATACC ATCTTCAACC TCTGCATTGA AAGTTCCCCA 300

ATTGAAAGTT GCAGAATCTG CCCAGAGTCC AGCTGCTGCT CATACTACTG ATACTGCTGG 360

GTATAATGCA ATGGAAGAAA GTGTGAGCAG GGAGAAGCCA GAATTGACAG CTTCAACAGA 420

AAGGGTCAAC AAAAGAATGT CCATGGTGGT GTCTGGCCTG ACCCCAGAAG AATTTGTGAG 480

TGTATCCATA TGTATCTCCC TAATGACTAA GACTTAACAA CATTCTGGAA AGAGTTTTAT 540

GTAGGTATTG TCAATTAATA ACCTAGAGGA AGAAATCTAG AAAACAATCA CAGTTCTGTG 600

TAATTTAATT TCGATTACTA ATTTCTGAAA ATTTAGAAY 639

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 922 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:27:

NCCCNNCCCC CNAATCTGAA ATGGGGGTAA CCCCCCCCCA ACCGANACNT GGGTNGCNTA 60

GAGANTTTAA TGGCCCNTTC TGAGGNACAN AAGCTTAAGC CAGGNGACGT GGANCNATGN 120

GTTGTTTNTT GTTTGGTTAC CTCCAGCCTG GGTGACAGAG CAAGACTCTG TCTAAAAAAA 180

-continued

AAAAAAAAAA AAATCGACTT TAAATAGTTC CAGGACACGT GTAGAACGTG CAGGATTGCT 240

ACGTAGGTAA ACATATGCCA TGGTGGGATA ACTAGTATTC TGAGCTGTGT GCTAGAGGTA 300

ACTCATGATA ATGGAATATT TGATTTAATT TCAGATGCTC GTGTACAAGT TTGCCAGAAA 360

ACACCACATC ACTTTAACTA ATCTAATTAC TGAAGAGACT ACTCATGTTG TTATGAAAAC 420

AGGTATACCA AGAACCTTTA CAGAATACCT TGCATCTGCT GCATAAAACC ACATGAGGCG 480

AGGCACGGTG GCGCATGCCT GTAATCGCAG CACTTTGGGA GGCCGAGGCG GGCAGATCAC 540

GAGATTAGGA GATCGAGACC ATCCTGGCCA GCATGGTGAA ACCCCGTCTC TACTANNAAA 600

TGGNAAAATT ANCTGGGTGT GGTCGCGTGC NCCTGTAGTC CCAGCTACTC GTGAGGCTGA 660

GGCAGGAGAA TCACTTGAAC CGGGGAAATG GAGGTTTCAG TGAGCAGAGA TCATNCCCCT 720

NCATTCCAGC CTGGCGACAG AGCAAGGCTC CGTCNCCNAA AAAATAAAAA AAAACGTGAA 780

CAAATAAGAA TATTTGTTGA GCATAGCATG GATGATAGTC TTCTAATAGT CAATCAATTA 840

CTTTATGAAA GACAAATAAT AGTTTTGCTG CTTCCTTACC TCCTTTTGTT TTGGGTTAAG 900

ATTTGGAGTG TGGGCCAGGC AC 922

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 867 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GATCTATAGC TAGCCTTGGC GTCTAGAAGA TGGGTGTTGA GAAGAGGGAG TGGAAAGATA 60

TTTCCTCTGG TCTTAACTTC ATATCAGCCT CCCCTAGACT TCCAAATATC CATACCTGCT 120

GGTTATAATT AGTGGTGTTT TCAGCCTCTG ATTCTGTCAC CAGGGGTTTT AGAATCATAA 180

ATCCAGATTG ATCTTGGGAG TGTAAAAAAC TGAGGCTCTT TAGCTTCTTA GGACAGCACT 240

TCCTGATTTT GTTTTCAACT TCTAATCCTT TGAGTGTTTT TCATTCTGCA GATGCTGAGT 300

TTGTGTGTGA ACGGACACTG AAATATTTTC TAGGAATTGC GGGAGGAAAA TGGGTAGTTA 360

GCTATTTCTG TAAGTATAAT ACTATTTCTC CCCTCCTCCC TTTAACACCT CAGAATTGCA 420

TTTTTACACC TAACATTTAA CACCTAAGGT TTTTGCTGAT GCTGAGTCTG AGTTACCAAA 480

AGGTCTTTAA ATTGTAATAC TAAACTACTT TTATCTTTAA TATCACTTTG TTCAAGATAA 540

GCTGGTGATG CTGGGAAAAT GGGTCTCTTT TATAACTAAT AGGACCTAAT CTGCTCCTAG 600

CAATGTTAGC ATATGAGCTA GGGATTTATT TAATAGTCGG CAGGAATCCA TGTGCARCAG 660

NCAAACTTAT AATGTTTAAA TTAAACATCA ACTCTGTCTC CAGAAGGAAA CTGCTGCTAC 720

AAGCCTTATT AAAGGGCTGT GGCTTTAGAG GGAAGGACCT CTCCTCTGTC ATTCTTCCTG 780

TGCTCTTTTG TGAATCGCTG ACCTCTCTAT CTCCGTGAAA AGAGCACGTT CTTCTGCTGT 840

ATGTAACCTG TCTTTTCTAT GATCTCT 867

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

-continued

(A) LENGTH: 561 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```
NAAAAACGGG GNNGGGANTG GGCCTTAAAN CCAAAGGGCN AACTCCCCAA CCATTNAAAA     60
ANTGACNGGG GATTATTAAA ANCGGCGGGA AACATTTCAC NGCCCAACTA ATATTGTTAA    120
ATTAAAACCA CCACCNCTGC NCCAAGGAGG GAAACTGCTG CTACAAGCCT TATTAAAGGG    180
CTGTGGCTTT AGAGGGAAGG ACCTCTCCTC TGTCATTCTT CCTGTGCTCT TTTGTGAATC    240
GCTGACCTCT CTATGTCCGT GAAAAGAGCA CGTTCTTCGT CTGTATGTAA CCTGTCTTTT    300
CTATGATCTC TTTAGGGGTG ACCCAGTCTA TTAAAGAAAG AAAAATGCTG AATGAGGTAA    360
GTACTTGATG TTACAAACTA ACCAGAGATA TTCATTCAGT CATATAGTTA AAAATGTATT    420
TGCTTCCTTC CATCAATGCA CCACTTTCCT TAACAATGCA CAAATTTTCC ATGATAATGA    480
GGATCATCAA GAATTATGCA GGCCTGCACT GTGGCTCATA CCTATAATCC CAGCGCTTTG    540
GGAGGCTGAG GCGCTTGGAT C                                              561
```

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 567 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```
AATTTTTTGT ATTTTTAGTA GAGATGAGGT TCACCATGTT GGTCTAGATC TGGTGTCGAA     60
CGTCCTGACC TCAAGTGATC TGCCAGCCTC AGTCTCCCAA AGTGCTAGGA TTACAGGGGT    120
GAGCCACTGC GCCTGGCCTG AATGCCTAAA ATATGACGTG TCTGCTCCAC TTCCATTGAA    180
GGAAGCTTCT CTTTCTCTTA TCCTGATGGG TTGTGTTTGG TTTCTTTCAG CATGATTTTG    240
AAGTCAGAGG AGATGTGGTC AATGGAAGAA ACCACCAAGG TCCAAAGCGA GCAAGAGAAT    300
CCCAGGACAG AAAGGTAAAG CTCCCTCCCT CAAGTTGACA AAAATCTCAC CCCACCACTC    360
TGTATTCCAC TCCCCTTTGC AGAGATGGGC CGCTTCATTT TGTAAGACTT ATTACATACA    420
TACACAGTGC TAGATACTTT CACACAGGTT CTTTTTTCAC TCTTCCATCC CAACCACATA    480
AATAAGTATT GTCTCTACTT TATGAATGAT AAAACTAAGA GATTTAGAGA GGCTGTGTAA    540
TTTGGATTCC CGTCTCGGGT TCAGATC                                        567
```

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

-continued

(A) LENGTH: 633 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
TTGGCCTGAT TGGTGACAAA AGTGAGATGC TCAGTCCTTG AATGACAAAG AATGCCTGTA     60
GAGTTGCAGG TCCAACTACA TATGCACTTC AAGAAGATCT TCTGAAATCT AGTAGTGTTC    120
TGGACATTGG ACTGCTTGTC CCTGGGAAGT AGCAGCAGAA ATGATCGGTG GTGAACAGAA    180
GAAAAAGAAA AGCTCTTCCT TTTTGAAAGT CTGTTTTTTG AATAAAAGCC AATATTCTTT    240
TATAACTAGA TTTTCCTTCT CTCCATTCCC CTGTCCCTCT CTCTTCCTCT CTTCTTCCAG    300
ATCTTCAGGG GGCTAGAAAT CTGTTGCTAT GGGCCCTTCA CCAACATGCC CACAGGTAAG    360
AGCCTGGGAG AACCCCAGAG TTCCAGCACC AGCCTTTGTC TTACATAGTG GAGTATTATA    420
AGCAAGGTCC CACGATGGGG GTTCCTCAGA TTGCTGAAAT GTTCTAGAGG CTATTCTATT    480
TCTCTACCAC TCTCCAAACA AAACAGCACC TAAATGTTAT CCTATGGCAA AAAAAAACTA    540
TACCTTGTCC CCCTTCTCAA GAGCATGAAG GTGGTTAATA GTTAGGATTC AGTATGTTAT    600
GTGTTCAGAT GGCGTTGAGC TGCTGTTAGT GCC                                 633
```

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 470 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:32:

```
TTTGAGAGAC TATCAAACCT TATACCAAGT GGCCTTATGG AGACTGATAA CCAGAGTACA     60
TGGCATATCA GTGGCAAATT GACTTAAAAT CCATACCCCT ACTATTTTAA GACCATTGTC    120
CTTTGGAGCA GAGAGACAGA CTCTCCCATT GAGAGGTCTT GCTATAAGCC TTCATCCGGA    180
GAGTGTAGGG TAGAGGGCCT GGGTTAAGTA TGCAGATTAC TGCAGTGATT TTACATGTAA    240
ATGTCCATTT TAGATCAACT GGAATGGATG GTACAGCTGT GTGGTGCTTC TGTGGTGAAG    300
GAGCTTTCAT CATTCACCCT TGGCACAGTA AGTATTGGGT GCCCTGTCAG TGTGGGAGGA    360
CACAATATTC TCTCCTGTGA GCAAGACTGG CACCTGTCAG TCCCTATGGA TGCCCCTACT    420
GTAGCCTCAG AAGTCTTCTC TGCCCACATA CCTGTGCCAA AAGACTCCAT               470
```

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 517 base pairs
(B) TYPE: nucleic acid

-continued

(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:33:

GGTGGTACGT GTCTGTAGTT CCAGCTACTT GGGAGGCTGA GATGGAAGGA TTGCTTGAGC 60

CCAGGAGGCA GAGGTGGNAN NTTACGCTGA GATCACACCA CTGCACTCCA GCCTGGGTGA 120

CAGAGCAAGA CCCTGTCTCA AAAACAAACA AAAAAAATGA TGAAGTGACA GTTCCAGTAG 180

TCCTACTTTG ACACTTTGAA TGCTCTTTCC TTCCTGGGGA TCCAGGGTGT CCACCCAATT 240

GTGGTTGTGC AGCCAGATGC CTGGACAGAG GACAATGGCT TCCATGGTAA GGTGCCTCGC 300

ATGTACCTGT GCTATTAGTG GGGTCCTTGT GCATGGGTTT GGTTTATCAC TCATTACCTG 360

GTGCTTGAGT AGCACAGTTC TTGGCACATT TTTAAATATT TGTTGAATGA ATGGCTAAAA 420

TGTCTTTTTG ATGTTTTTAT TGTTATTTGT TTTATATTGT AAAAGTAATA CATGAACTGT 480

TTCCATGGGG TGGGAGTAAG ATATGAATGT TCATCAC 517

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 434 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:34:

CAGTAATCCT NAGAACTCAT ACGACCGGGC CCCTGGAGTC GNTGNTTNGA GCCTAGTCCN 60

GGAGAATGAA TTGACACTAA TCTCTGCTTG TGTTCTCTGT CTCCAGCAAT TGGGCAGATG 120

TGTGAGGCAC CTGTGGTGAC CCGAGAGTGG GTGTTGGACA GTGTAGCACT CTACCAGTGC 180

CAGGAGCTGG ACACCTACCT GATACCCCAG ATCCCCCACA GCCACTACTG ACTGCAGCCA 240

GCCACAGGTA CAGAGCCACA GGACCCCAAG AATGAGCTTA CAAAGTGGCC TTTCCAGGCC 300

CTGGGAGCTC CTCTCACTCT TCAGTCCTTC TACTGTCCTG GCTACTAAAT ATTTTATGTA 360

CATCAGCCTG AAAAGGACTT CTGGCTATGC AAGGGTCCCT TAAAGATTTT CTGCTTGAAG 420

TCTCCCTTGG AAAT 434

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

-continued

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

GATAAATTAA AACTGCGACT GCGCGGCGTG 30

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GTAGTAGAGT CCCGGGAAAG GGACAGGGGG 30

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

ATATATATAT GTTTTTCTAA TGTGTTAAAG 30

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

GTAAGTCAGC ACAAGAGTGT ATTAATTTGG 30

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

-continued

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:39:

TTTCTTTTTC TCCCCCCCCT ACCCTGCTAG 30

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:40:

GTAAGTTTGA ATGTGTTATG TGGCTCCATT 30

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:41:

AGCTACTTTT TTTTTTTTTT TTTGAGACAG 30

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:42:

GTAAGTGCAC ACCACCATAT CCAGCTAAAT 30

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:43:

AATTGTTCTT TCTTTCTTTA TAATTTATAG 30

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:44:

GTATATAATT TGGTAATGAT GCTAGGTTGG 30

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:45:

GAGTGTGTTT CTCAAACAAT TTAATTTCAG 30

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:46:

GTAAGTGTTG AATATCCCAA GAATGACACT 30

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:47:

AAACATAATG TTTTCCCTTG TATTTTACAG 30

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:48:

GTAAAACCAT TTGTTTTCTT CTTCTTCTTC 30

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:49:

TGCTTGACTG TTCTTTACCA TACTGTTTAG 30

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:50:

GTAAGGGTCT CAGGTTTTTT AAGTATTTAA 30

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

TGATTTATTT TTTGGGGGGA AATTTTTTAG 30

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

GTGAGTCAAA GAGAACCTTT GTCTATGAAG 30

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

TCTTATTAGG ACTCTGTCTT TTCCCTATAG 30

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

GTAATGGCAA AGTTTGCCAA CTTAACAGGC 30

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:55:

GAGTACCTTG TTATTTTTGT ATATTTTCAG 30

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:56:

GTATTGGAAC CAGGTTTTTG TGTTTGCCCC 30

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:57:

ACATCTGAAC CTCTGTTTTT GTTATTTAAG 30

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:58:

AGGTAAAAAG CGTGTGTGTG TGTGCACATG 30

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:59:

CATTTTCTTG GTACCATTTA TCGTTTTTGA 30

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:60:

GTGTGTATTG TTGGCCAAAC ACTGATATCT 30

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:61:

AGTAGATTTG TTTTCTCATT CCATTTAAAG 30

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:62:

GTAAGAAACA TCAATGTAAA GATGCTGTGG 30

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:63:

ATGGTTTTCT CCTTCCATTT ATCTTTCTAG 30

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:64:

GTAATATTTC ATCTGCTGTA TTGGAACAAA 30

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:65:

TGTAAATTAA ACTTCTCCCA TTCCTTTCAG 30

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:66:

GTGAGTGTAT CCATATGTAT CTCCCTAATG 30

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

-continued

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:67:

ATGATAATGG AATATTTGAT TTAATTTCAG 30

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:68:

GTATACCAAG AACCTTTACA GAATACCTTG 30

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:69:

CTAATCCTTT GAGTGTTTTT CATTCTGCAG 30

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:70:

GTAAGTATAA TACTATTTCT CCCCTCCTCC 30

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

-continued

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:71:

TGTAACCTGT CTTTTCTATG ATCTCTTTAG 30

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:72:

GTAAGTACTT GATGTTACAA ACTAACCAGA 30

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:73:

TCCTGATGGG TTGTGTTTGG TTTCTTTCAG 30

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:74:

GTAAAGCTCC CTCCCTCAAG TTGACAAAAA 30

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

-continued

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:75:

CTGTCCCTCT CTCTTCCTCT CTTCTTCCAG 30

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:76:

GTAAGAGCCT GGGAGAACCC CAGAGTTCCA 30

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:77:

AGTGATTTTA CATGTAAATG TCCATTTTAG 30

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:78:

GTAAGTATTG GGTGCCCTGT CAGTGTGGGA 30

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

-continued

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:79:

TTGAATGCTC TTTCCTTCCT GGGGATCCAG 30

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:80:

GTAAGGTGCC TCGCATGTAC CTGTGCTATT 30

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:81:

CTAATCTCTG CTTGTGTTCT CTGTCTCCAG 30

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: peptide

(i i i) HYPOTHETICAL: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:82:

```
Cys Pro Ile Cys Leu Glu Leu Ile Lys Glu Pro Val Ser Thr Lys Cys
1               5                   10                  15

Asp His Ile Phe Cys Lys Phe Cys Met Leu Lys Leu Leu Asn Gln Lys
            20                  25                  30

Lys Gly Pro Ser Gln Cys Pro Leu Cys Lys
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 amino acids

-continued

(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: peptide

(i i i) HYPOTHETICAL: NO

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:83:

```
Cys Pro Ile Cys Leu Glu Leu Leu Lys Gln Pro Val Ser Ala Asp Cys
1               5                   10                  15

Asn His Ser Phe Cys Arg Ala Cys Ile Thr Leu Asn Tyr Glu Ser Asn
            20                  25                  30

Arg Asn Thr Asp Gly Lys Gly Asn Cys Pro Val Cys Arg
        35                  40                  45
```

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 41 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: peptide

(i i i) HYPOTHETICAL: NO

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:84:

```
Cys Pro Ile Cys Leu Asp Met Leu Lys Asn Thr Met Thr Thr Lys Glu
1               5                   10                  15

Cys Leu His Arg Phe Cys Ser Asp Cys Ile Val Thr Ala Leu Arg Ser
            20                  25                  30

Gly Asn Lys Glu Cys Pro Thr Cys Arg
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: peptide

(i i i) HYPOTHETICAL: NO

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:85:

```
Cys Pro Val Cys Leu Gln Tyr Phe Ala Glu Pro Met Met Leu Asp Cys
1               5                   10                  15

Gly His Asn Ile Cys Cys Ala Cys Leu Ala Arg Cys Trp Gly Thr Ala
            20                  25                  30

Cys Thr Asn Val Ser Cys Pro Gln Cys Arg
        35                  40
```

What is claimed is:

1. An isolated DNA comprising an altered BRCA1 DNA having at least one of the alterations set forth in Tables 12A, 14, 18 or 19 with the proviso that the alteration is not a deletion of four nucleotides corresponding to base numbers 4184–4187 in SEQ. ID. NO:1.

2. An isolated DNA comprising an altered BRCA1 DNA having one of the alterations set forth in Tables 12A or 14 with the provision that the alteration is not a deletion of four nucleotides corresponding to base numbers 4184–4187 in SEQ. ID. NO:1.

3. An isolated DNA comprising an altered BRCA1 DNA having one of the alterations set forth in Tables 18 or 19.

4. A nucleic acid probe specifically hybridizable to a human altered BRCA1 DNA and not to wild-type BRCA1 DNA, said altered BRCA1 DNA having one of the alterations set forth in Tables, 12A, 14, 18 or 19.

5. A nucleic acid probe specifically hybridizable to human altered BRCA1 DNA and not to wild-type BRCA1 DNA, said altered BRCA1 DNA having one of the alterations set forth in Tables 12A or 14 with the proviso that the alteration

is not a deletion of four nucleotides corresponding to base numbers 4184–4187 in SEQ. ID. NO:1.

6. A nucleic acid probe specifically hybridizable to human altered BRCA1 DNA and not to wild-type BRCA1 DNA, said altered BRCA1 DNA having one of the alterations set forth in Tables 18 or 19.

7. The nucleic acid probe of claim 6 wherein said altered BRCA1 DNA has the alteration comprising a deletion of AG in codon 23.

8. The nucleic acid probe of claim 6 wherein said altered BRCA1 DNA has the alteration comprising an insertion of a nucleotide C corresponding to a base number 5382 in SEQ ID NO:1.

9. The nucleic acid probe of claim 6 wherein said altered BRCA1 DNA has the alteration comprising a deletion of 40 nucleotides corresponding to base numbers 1294–1333 of SEQ ID NO:1.

10. The nucleic acid probe of claim 6 wherein said altered BRCA1 DNA has the ablation comprising a substitution of a G for the T corresponding to a base number 391 in SEQ ID NO:17.

11. The isolated DNA of claim 2 wherein said altered BRCA1 DNA has the alteration comprising a deletion of AG in codon 23.

12. The isolated DNA of claim 2 wherein said altered BRCA1 DNA has the alteration comprising an insertion of a nucleotide C corresponding to a base number 5382 in SEQ ID NO:1.

13. The isolated DNA of claim 2 wherein said altered BRCA1 DNA has the alteration comprising a deletion of 40 nucleotides corresponding to base numbers 1294–1333 in SEQ ID NO:1.

14. The isolated DNA of claim 2 wherein said altered BRCA1 DNA has the alteration comprising a substitution of a G for the T corresponding to a base number 391 in SEQ ID NO:17.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,693,473 Page 1 of 2

DATED : 02 December 1997

INVENTOR(S) : Donna M. SHATTUCK-EIDENS et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 1, line 67, "minors" should be -- tumors --.

Col. 2, line 9, "minor" should be -- tumor --.

Col. 4, line 18, "dam" should be -- data --.

Col. 6, line 25, "drags" should be -- drugs --.

Col. 6, line 27, "gone" should be -- gene --.

Col. 20, line 42, "Biotec" should be -- Biotech --.

Col. 28, lines 53-54, "Denamration" should be -- Denaturation --.

Col. 30, line 57, "drag" should be -- drug --.

Col. 31, line 60, "drag" should be -- drug --.

Col. 32, line 63, "carrier" should be -- carried --

Col. 36, line 23-24, "collaborators" should be **--collaborators'--.**

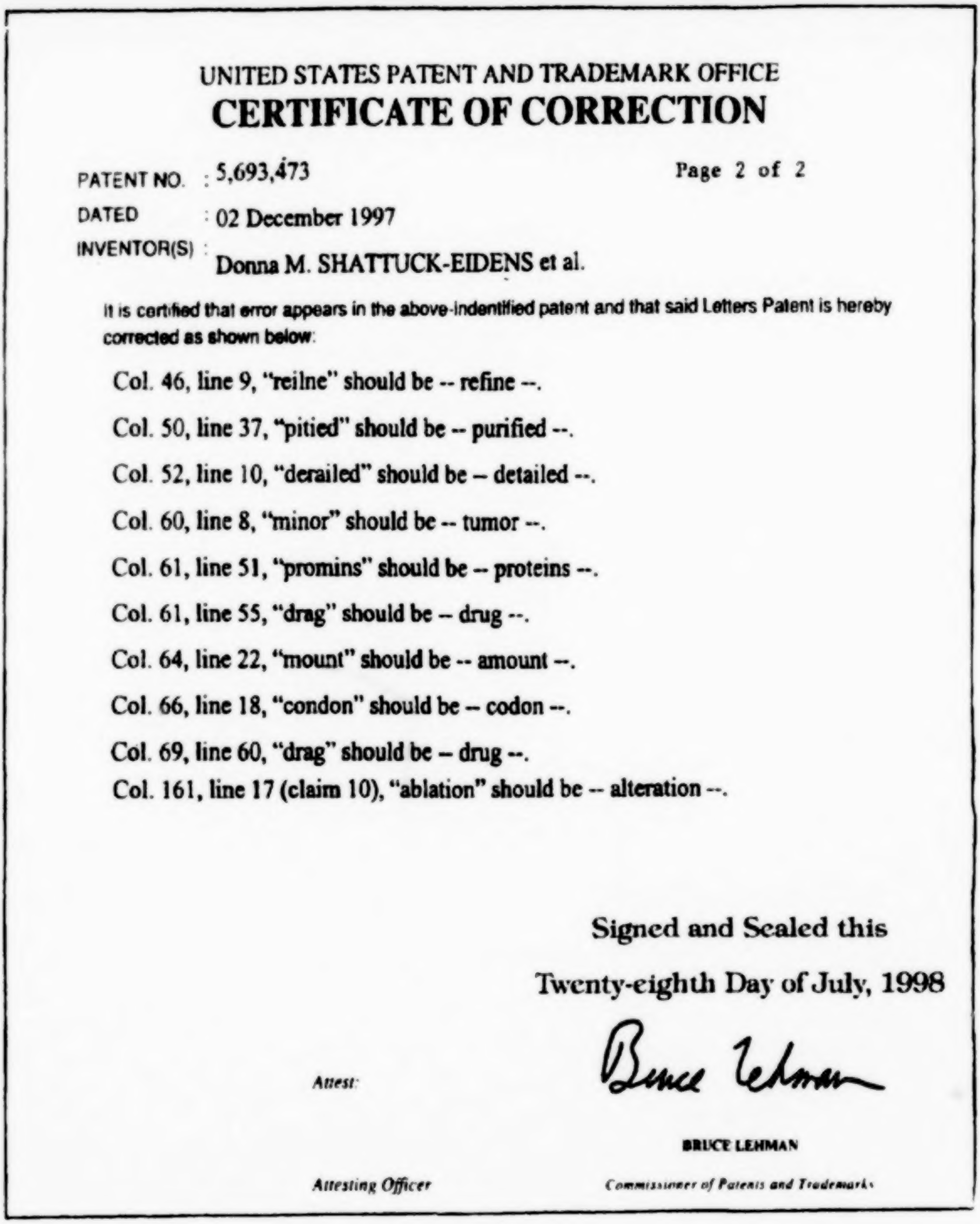
Col. 37, line 4, "romaround" should be -- turnaround --.

Col. 37, line 9, "ann" should be -- arm --.

Col. 38, line 34, "Mfd5" should be -- Mfd15 --.

Col. 38, line 43, "Mfd5" should be -- Mfd15 --.

Col. 39, line 57, "exand ag" should be -- existing --.



UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,693,473 Page 2 of 2

DATED : 02 December 1997

INVENTOR(S) : Donna M. SHATTUCK-EIDENS et al.

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Col. 46, line 9, "reilne" should be -- refine --.

Col. 50, line 37, "pitied" should be -- purified --.

Col. 52, line 10, "derailed" should be -- detailed --.

Col. 60, line 8, "minor" should be -- tumor --.

Col. 61, line 51, "promins" should be -- proteins --.

Col. 61, line 55, "drag" should be -- drug --.

Col. 64, line 22, "mount" should be -- amount --.

Col. 66, line 18, "condon" should be -- codon --.

Col. 69, line 60, "drag" should be -- drug --.

Col. 161, line 17 (claim 10), "ablation" should be -- alteration --.

Signed and Sealed this

Twenty-eighth Day of July, 1998

Attest:

Bruce Lehman

BRUCE LEHMAN

Attesting Officer *Commissioner of Patents and Trademarks*

PATENT '492

US005837492A

United States Patent [19]

Tavtigian et al.

[11] **Patent Number: 5,837,492**

[45] **Date of Patent: Nov. 17, 1998**

[54] **CHROMOSOME 13-LINKED BREAST CANCER SUSCEPTIBILITY GENE**

[75] Inventors: **Sean V. Tavtigian**; **Alexander Kamb**, both of Salt Lake City, Utah; **Jacques Simard**, St. Augustin de Desmuures, Canada; **Fergus Couch**, St. Davids, Pa.; **Johanna M. Rommens**, Toronto, Canada; **Barbara L. Weber**, Merion, Pa.

[73] Assignees: **Myriad Genetics, Inc.**, Salt Lake City, Utah; **Endo Recherche, Inc.**, Sainte-Foy, Canada; **HSC Research & Development Limited Partnership**, Toronto, Canada; **Trustees of the University of Pennsylvaina**, Philadelphia, Pa.

[21] Appl. No.: **639,501**

[22] Filed: **Apr. 29, 1996**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 585,391, Jan. 11, 1996, abandoned, which is a continuation-in-part of Ser. No. 576,559, Dec. 21, 1995, abandoned, which is a continuation-in-part of Ser. No. 575,359, Dec. 20, 1995, abandoned, which is a continuation-in-part of Ser. No. 573,779, Dec. 18, 1995, abandoned.

[51] **Int. Cl.^{6}** **C12N 15/63**, C12N 15/79, C12N 15/09; C12N 5/10

[52] **U.S. Cl.** **435/69.1**; 435/320.1; 435/375; 435/172.3; 530/828; 935/62; 935/70; 935/71; 935/34

[58] **Field of Search** 435/320.1, 375, 435/6, 172.3, 69.1; 530/828, 350; 935/62, 52, 34, 71, 70, 33, 65

[56] **References Cited**

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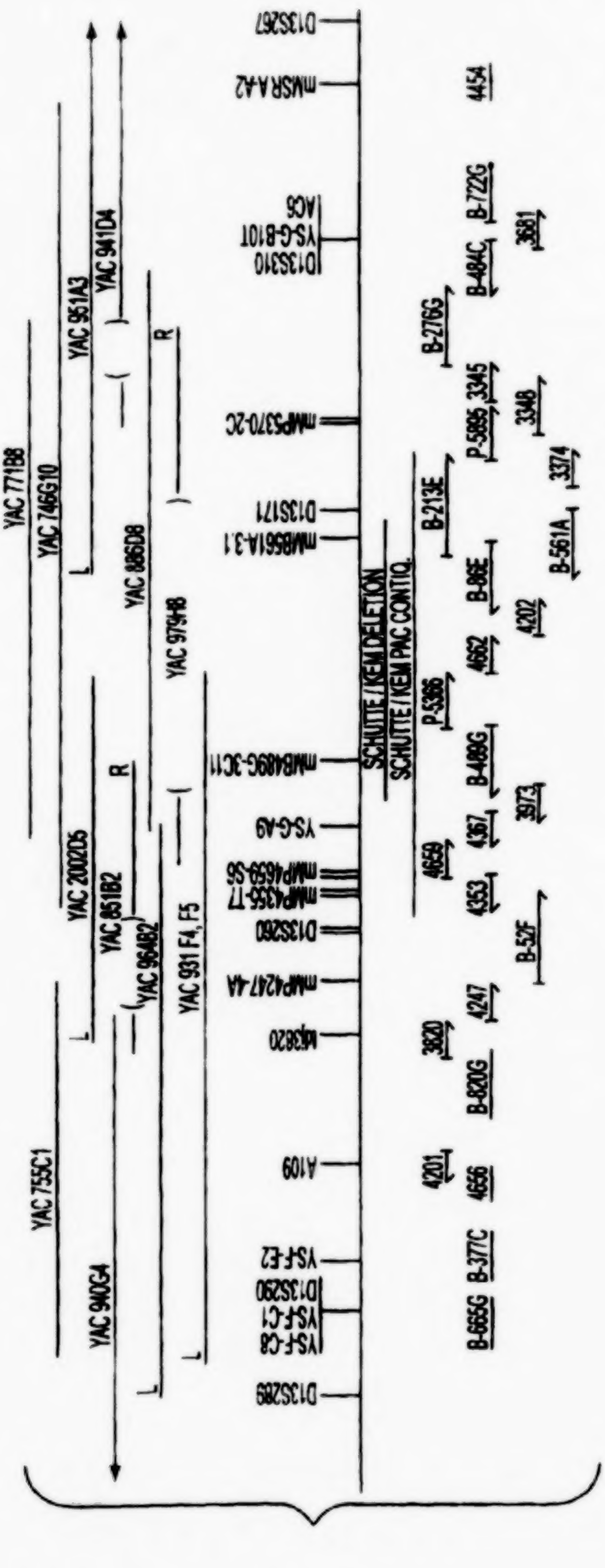
Primary Examiner—Jasemine C. Chambers
Assistant Examiner—Karen M. Hauda
Attorney, Agent, or Firm—Rothwell, Figg, Ernst & Kurz, P.C.

[57] **ABSTRACT**

The present invention relates generally to the field of human genetics. Specifically, the present invention relates to methods and materials used to isolate and detect a human breast cancer predisposing gene (BRCA2), some mutant alleles of which cause susceptibility to cancer, in particular breast cancer. More specifically, the invention relates to germline mutations in the BRCA2 gene and their use in the diagnosis of predisposition to breast cancer. The present invention further relates to somatic mutations in the BRCA2 gene in human breast cancer and their use in the diagnosis and prognosis of human breast cancer. Additionally, the invention relates to somatic mutations in the BRCA2 gene in other human cancers and their use in the diagnosis and prognosis of human cancers. The invention also relates to the therapy of human cancers which have a mutation in the BRCA2 gene, including gene therapy, protein replacement therapy and protein mimetics. The invention further relates to the screening of drugs for cancer therapy. Finally, the invention relates to the screening of the BRCA2 gene for mutations, which are useful for diagnosing the predisposition to breast cancer.

30 Claims, 9 Drawing Sheets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SCHUTTE / KEM DELETION
SCHUTTE / KEM PAC CONTIG.
B-276G
B-213E
P-5386
4659
3820
4201
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B-722G
B-484C
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B-86E
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4353
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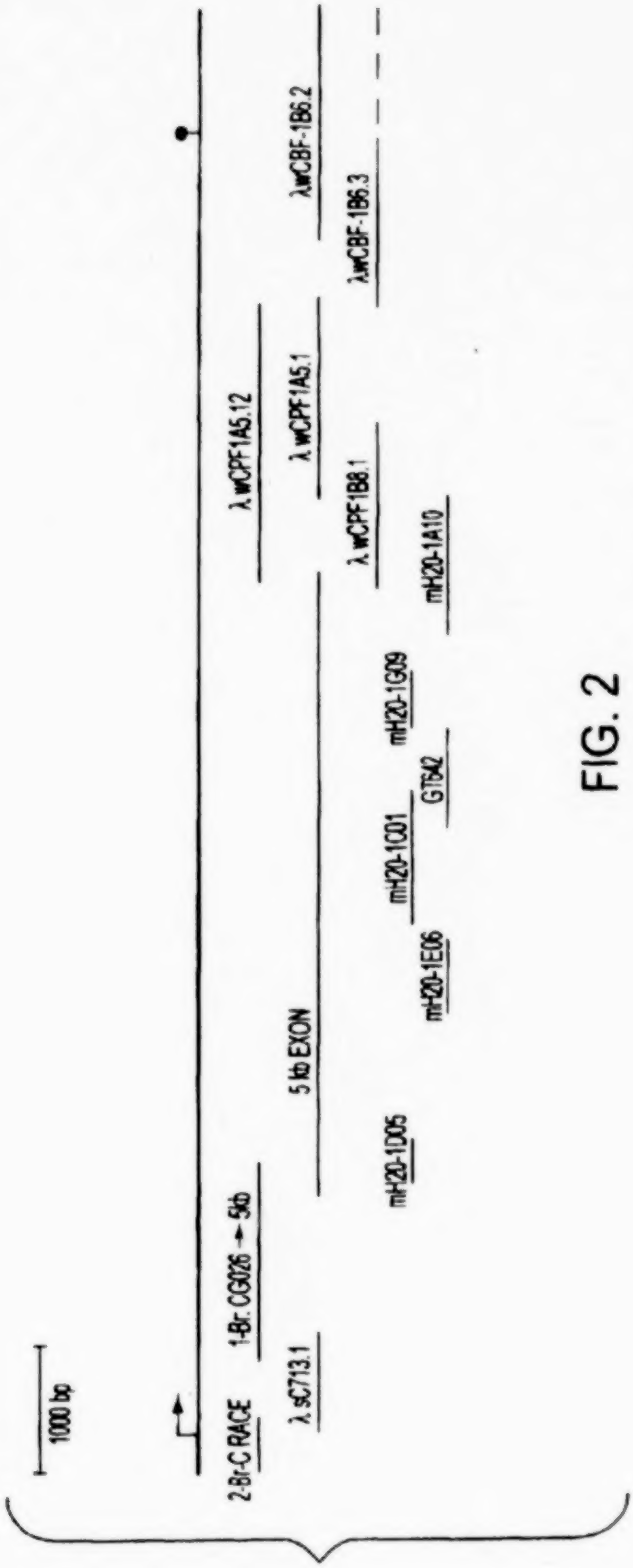
4202
3973
B-52F

FIG. 1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λ sC713.1
1-Br: CG026 → 5kb
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GT642
mH20-1G09
mH20-1A10
λ wCPF1B8.1
λ wCPF1A5.1
λ wCPF1A5.12
λwCBF-1B6.3
λwCBF-1B6.2

FIG. 2

1 GGTGGCGCGA GCTTCTGAAA CTAGGCGGCA GAGGCGGAGC CGCTGTGGCA CTGCTGCGCC
61 TCTGCTGCGC CTCGGGTGTC TTTTGCGGCG GTGGGTCGCC GCCGGGAGAA GCGTGAGGGG
121 ACAGATTTGT GACCGGCGCG GTTTTTGTCA GCTTACTCCG GCCAAAAAAG AACTGCACCT
181 CTGGAGCGGA CTTATTTACC AAGCATTGGA GGAATATCGT AGGTAAAAAT GCCTATTGGA
241 TCCAAAGAGA GGCCAACATT TTTTGAAATT TTTAAGACAC GCTGCAACAA AGCAGATTTA
301 GGACCAATAA GTCTTAATTG GTTTGAAGAA CTTTCTTCAG AAGCTCCACC CTATAATTCT
361 GAACCTGCAG AAGAATCTGA ACATAAAAAC AACAATTACG AACCAAACCT ATTTAAAACT
421 CCACAAAGGA AACCATCTTA TAATCAGCTG GCTTCAACTC CAATAATATT CAAAGAGCAA
481 GGGCTGACTC TGCCGCTGTA CCAATCTCCT GTAAAAGAAT TAGATAAATT CAAATTAGAC
541 TTAGGAAGGA ATGTTCCCAA TAGTAGACAT AAAAGTCTTC GCACAGTGAA AACTAAAATG
601 GATCAAGCAG ATGATGTTTC CTGTCCACTT CTAAATTCTT GTCTTAGTGA AAGTCCTGTT
661 GTTCTACAAT GTACACATGT AACACCACAA AGAGATAAGT CAGTGGTATG TGGGAGTTTG
721 TTTCATACAC CAAAGTTTGT GAAGGGTCGT CAGACACCAA AACATATTTC TGAAAGTCTA
781 GGAGCTGAGG TGGATCCTGA TATGTCTTGG TCAAGTTCTT TAGCTACACC ACCCACCCTT
841 AGTTCTACTG TGCTCATAGT CAGAAATGAA GAAGCATCTG AAACTGTATT TCCTCATGAT
901 ACTACTGCTA ATGTGAAAAG CTATTTTTCC AATCATGATG AAAGTCTGAA GAAAAATGAT
961 AGATTTATCG CTTCTGTGAC AGACAGTGAA AACACAAATC AAAGAGAAGC TGCAAGTCAT
1021 GGATTTGGAA AAACATCAGG GAATTCATTT AAAGTAAATA GCTGCAAAGA CCACATTGGA
1081 AAGTCAATGC CAAATGTCCT AGAAGATGAA GTATATGAAA CAGTTGTAGA TACCTCTGAA
1141 GAAGATAGTT TTTCATTATG TTTTTCTAAA TGTAGAACAA AAAATCTACA AAAAGTAAGA
1201 ACTAGCAAGA CTAGGAAAAA AATTTTCCAT GAAGCAAACG CTGATGAATG TGAAAAATCT
1261 AAAAACCAAG TGAAAGAAAA ATACTCATTT GTATCTGAAG TGGAACCAAA TGATACTGAT
1321 CCATTAGATT CAAATGTAGC ACATCAGAAG CCCTTTGAGA GTGGAAGTGA CAAAATCTCC
1381 AAGGAAGTTG TACCGTCTTT GGCCTGTGAA TGGTCTCAAC TAACCCTTTC AGGTCTAAAT
1441 GGAGCCCAGA TGGAGAAAAT ACCCCTATTG CATATTTCTT CATGTGACCA AAATATTTCA
1501 GAAAAAGACC TATTAGACAC AGAGAACAAA AGAAAGAAAG ATTTTCTTAC TTCAGAGAAT
1561 TCTTTGCCAC GTATTTCTAG CCTACCAAAA TCAGAGAAGC CATTAAATGA GGAAACAGTG
1621 GTAAATAAGA GAGATGAAGA GCAGCATCTT GAATCTCATA CAGACTGCAT TCTTGCAGTA
1681 AAGCAGGCAA TATCTGGAAC TTCTCCAGTG GCTTCTTCAT TTCAGGGTAT CAAAAAGTCT
1741 ATATTCAGAA TAAGAGAATC ACCTAAAGAG ACTTTCAATG CAAGTTTTTC AGGTCATATG
1801 ACTGATCCAA ACTTTAAAAA AGAAACTGAA GCCTCTGAAA GTGGACTGGA AATACATACT
1861 GTTTGCTCAC AGAAGGAGGA CTCCTTATGT CCAAATTTAA TTGATAATGG AAGCTGGCCA
1921 GCCACCACCA CACAGAATTC TGTAGCTTTG AAGAATGCAG GTTTAATATC CACTTTGAAA
1981 AAGAAAACAA ATAAGTTTAT TTATGCTATA CATGATGAAA CATCTTATAA AGGAAAAAAA
2041 ATACCGAAAG ACCAAAAATC AGAACTAATT AACTGTTCAG CCCAGTTTGA AGCAAATGCT
2101 TTTGAAGCAC CACTTACATT TGCAAATGCT GATTCAGGTT TATTGCATTC TTCTGTGAAA
2161 AGAAGCTGTT CACAGAATGA TTCTGAAGAA CCAACTTTGT CCTTAACTAG CTCTTTTGGG
2221 ACAATTCTGA GGAAATGTTC TAGAAATGAA ACATGTTCTA ATAATACAGT AATCTCTCAG
2281 GATCTTGATT ATAAAGAAGC AAAATGTAAT AAGGAAAAAC TACAGTTATT TATTACCCCA
2341 GAAGCTGATT CTCTGTCATG CCTGCAGGAA GGACAGTGTG AAAATGATCC AAAAAGCAAA
2401 AAAGTTTCAG ATATAAAAGA AGAGGTCTTG GCTGCAGCAT GTCACCCAGT ACAACATTCA
2461 AAAGTGGAAT ACAGTGATAC TGACTTTCAA TCCCAGAAAA GTCTTTTATA TGATCATGAA
2521 AATGCCAGCA CTCTTATTTT AACTCCTACT TCCAAGGATG TTCTGTCAAA CCTAGTCATG
2581 ATTTCTAGAG GCAAAGAATC ATACAAAATG TCAGACAAGC TCAAAGGTAA CAATTATGAA
2641 TCTGATGTTG AATTAACCAA AAATATTCCC ATGGAAAAGA ATCAAGATGT ATGTGCTTTA
2701 AATGAAAATT ATAAAAACGT TGAGCTGTTG CCACCTGAAA AATACATGAG AGTAGCATCA
2761 CCTTCAAGAA AGGTACAATT CAACCAAAAC ACAAATCTAA GAGTAATCCA AAAAAATCAA
2821 GAAGAAACTA CTTCAATTTC AAAAATAACT GTCAATCCAG ACTCTGAAGA ACTTTTCTCA
2881 GACAATGAGA ATAATTTTGT CTTCCAAGTA GCTAATGAAA GGAATAATCT TGCTTTAGGA
2941 AATACTAAGG AACTTCATGA AACAGACTTG ACTTGTGTAA ACGAACCCAT TTTCAAGAAC
3001 TCTACCATGG TTTTATATGG AGACACAGGT GATAAACAAG CAACCCAAGT GTCAATTAAA
3061 AAAGATTTGG TTTATGTTCT TGCAGAGGAG AACAAAAATA GTGTAAAGCA GCATATAAAA
3121 ATGACTCTAG GTCAAGATTT AAAATCGGAC ATCTCCTTGA ATATAGATAA AATACCAGAA
3181 AAAAATAATG ATTACATGAA CAAATGGGCA GGACTCTTAG GTCCAATTTC AAATCACAGT
3241 TTTGGAGGTA GCTTCAGAAC AGCTTCAAAT AAGGAAATCA AGCTCTCTGA ACATAACATT

FIG. 3A

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3301 AAGAAGAGCA AAATGTTCTT CAAAGATATT GAAGAACAAT ATCCTACTAG TTTAGCTTGT
3361 GTTGAAATTG TAAATACCTT GGCATTAGAT AATCAAAAGA AACTGAGCAA GCCTCAGTCA
3421 ATTAATACTG TATCTGCACA TTTACAGAGT AGTGTAGTTG TTTCTGATTG TAAAAATAGT
3481 CATATAACCC CTCAGATGTT ATTTTCCAAG CAGGATTTTA ATTCAAACCA TAATTTAACA
3541 CCTAGCCAAA AGGCAGAAAT TACAGAACTT TCTACTATAT TAGAAGAATC AGGAAGTCAG
3601 TTTGAATTTA CTCAGTTTAG AAAACCAAGC TACATATTGC AGAAGAGTAC ATTTGAAGTG
3661 CCTGAAAACC AGATGACTAT CTTAAAGACC ACTTCTGAGG AATGCAGAGA TGCTGATCTT
3721 CATGTCATAA TGAATGCCCC ATCGATTGGT CAGGTAGACA GCAGCAAGCA ATTTGAAGGT
3781 ACAGTTGAAA TTAAACGGAA GTTTGCTGGC CTGTTGAAAA ATGACTGTAA CAAAAGTGCT
3841 TCTGGTTATT TAACAGATGA AAATGAAGTG GGGTTTAGGG GCTTTTATTC TGCTCATGGC
3901 ACAAAACTGA ATGTTTCTAC TGAAGCTCTG CAAAAAGCTG TGAAACTGTT TAGTGATATT
3961 GAGAATATTA GTGAGGAAAC TTCTGCAGAG GTACATCCAA TAAGTTTATC TTCAAGTAAA
4021 TGTCATGATT CTGTTGTTTC AATGTTTAAG ATAGAAAATC ATAATGATAA AACTGTAAGT
4081 GAAAAAAATA ATAAATGCCA ACTGATATTA CAAAATAATA TTGAAATGAC TACTGGCACT
4141 TTTGTTGAAG AAATTACTGA AAATTACAAG AGAAATACTG AAAATGAAGA TAACAAATAT
4201 ACTGCTGCCA GTAGAAATTC TCATAACTTA GAATTTGATG GCAGTGATTC AAGTAAAAAT
4261 GATACTGTTT GTATTCATAA AGATGAAACG GACTTGCTAT TTACTGATCA GCACAACATA
4321 TGTCTTAAAT TATCTGGCCA GTTTATGAAG GAGGGAAACA CTCAGATTAA AGAAGATTTG
4381 TCAGATTTAA CTTTTTTGGA AGTTGCGAAA GCTCAAGAAG CATGTCATGG TAATACTTCA
4441 AATAAAGAAC AGTTAACTGC TACTAAAACG GAGCAAAATA TAAAAGATTT TGAGACTTCT
4501 GATACATTTT TTCAGACTGC AAGTGGGAAA AATATTAGTG TCGCCAAAGA GTCATTTAAT
4561 AAAATTGTAA ATTTCTTTGA TCAGAAACCA GAAGAATTGC ATAACTTTTC CTTAAATTCT
4621 GAATTACATT CTGACATAAG AAAGAACAAA ATGGACATTC TAAGTTATGA GGAAACAGAC
4681 ATAGTTAAAC ACAAAATACT GAAAGAAAGT GTCCCAGTTG GTACTGGAAA TCAACTAGTG
4741 ACCTTCCAGG GACAACCCGA ACGTGATGAA AAGATCAAAG AACCTACTCT GTTGGGTTTT
4801 CATACAGCTA GCGGGAAAAA AGTTAAAATT GCAAAGGAAT CTTTGGACAA AGTGAAAAAC
4861 CTTTTTGATG AAAAAGAGCA AGGTACTAGT GAAATCACCA GTTTTAGCCA TCAATGGGCA
4921 AAGACCCTAA AGTACAGAGA GGCCTGTAAA GACCTTGAAT TAGCATGTGA GACCATTGAG
4981 ATCACAGCTG CCCCAAAGTG TAAAGAAATG CAGAATTCTC TCAATAATGA TAAAAACCTT
5041 GTTTCTATTG AGACTGTGGT GCCACCTAAG CTCTTAAGTG ATAATTTATG TAGACAAACT
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5521 AAAAATAAAC TTGATTCTGG TATTGAGCCA GTATTGAAGA ATGTTGAAGA TCAAAAAAAC
5581 ACTAGTTTTT CCAAAGTAAT ATCCAATGTA AAAGATGCAA ATGCATACCC ACAAACTGTA
5641 AATGAAGATA TTTGCGTTGA GGAACTTGTG ACTAGCTCTT CACCCTGCAA AAATAAAAAT
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6421 CAAGTTTCCA TTTTAGAAAG TTCCTTACAC AAAGTTAAGG GAGTGTTAGA GGAATTTGAT
6481 TTAATCAGAA CTGAGCATAG TCTTCACTAT TCACCTACGT CTAGACAAAA TGTATCAAAA
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FIG. 3B

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6541 ATACTTCCTC GTGTTGATAA GAGAAACCCA GAGCACTGTG TAAACTCAGA AATGGAAAAA
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6661 AATAATCACT CTATTAAAGT TTCTCCATAT CTCTCTCAAT TTCAACAAGA CAAACAACAG
6721 TTGGTATTAG GAACCAAAGT CTCACTTGTT GAGAACATTC ATGTTTTGGG AAAAGAACAG
6781 GCTTCACCTA AAAACGTAAA AATGGAAATT GGTAAAACTG AAACTTTTTC TGATGTTCCT
6841 GTGAAAACAA ATATAGAAGT TTGTTCTACT TACTCCAAAG ATTCAGAAAA CTACTTTGAA
6901 ACAGAAGCAG TAGAAATTGC TAAAGCTTTT ATGGAAGATG ATGAACTGAC AGATTCTAAA
6961 CTGCCAAGTC ATGCCACACA TTCTCTTTTT ACATGTCCCG AAAATGAGGA AATGGTTTTG
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7621 GCAGCAGCTG TAACTTTCAC AAAGTGTGAA GAAGAACCTT TAGATTTAAT TACAAGTCTT
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7921 GAAGATTATT TTGGTAAGGA AAGTTTATGG ACTGGAAAAG GAATACAGTT GGCTGATGGT
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8521 TGTACACCTC TTGAAGCCCC AGAATCTCTT ATGTTAAAGA TTTCTGCTAA CAGTACTCGG
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8641 TTATCATCGC TTTTCAGTGA TGGAGGAAAT GTTGGTTGTG TTGATGTAAT TATTCAAAGA
8701 GCATACCCTA TACAGTGGAT GGAGAAGACA TCATCTGGAT TATACATATT TCGCAATGAA
8761 AGAGAGGAAG AAAAGGAAGC AGCAAAATAT GTGGAGGCCC AACAAAAGAG ACTAGAAGCC
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8881 TTACCATCAC GTGCACTAAC AAGACAGCAA GTTCGTGCTT TGCAAGATGG TGCAGAGCTT
8941 TATGAAGCAG TGAAGAATGC AGCAGACCCA GCTTACCTTG AGGGTTATTT CAGTGAAGAG
9001 CAGTTAAGAG CCTTGAATAA TCACAGGCAA ATGTTGAATG ATAAGAAACA AGCTCAGATC
9061 CAGTTGGAAA TTAGGAAGGC CATGGAATCT GCTGAACAAA AGGAACAAGG TTTATCAAGG
9121 GATGTCACAA CCGTGTGGAA GTTGCGTATT GTAAGCTATT CAAAAAAAGA AAAAGATTCA
9181 GTTATACTGA GTATTTGGCG TCCATCATCA GATTTATATT CTCTGTTAAC AGAAGGAAAG
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9421 TTTCAGCCAT CTTGTTCTGA GGTGGACCTA ATAGGATTTG TCGTTTCTGT TGTGAAAAAA
9481 ACAGGACTTG CCCCTTTCGT CTATTTGTCA GACGAATGTT ACAATTTACT GGCAATAAAG
9541 TTTTGGATAG ACCTTAATGA GGACATTATT AAGCCTCATA TGTTAATTGC TGCAAGCAAC
9601 CTCCAGTGGC GACCAGAATC CAAATCAGGC CTTCTTACTT TATTTGCTGG AGATTTTTCT
9661 GTGTTTTCTG CTAGTCCAAA AGAGGGCCAC TTTCAAGAGA CATTCAACAA AATGAAAAAT
9721 ACTGTTGAGA ATATTGACAT ACTTTGCAAT GAAGCAGAAA ACAAGCTTAT GCATATACTG
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FIG. 3C

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 9781 CATGCAAATG ATCCCAAGTG GTCCACCCCA ACTAAAGACT GTACTTCAGG GCCGTACACT
 9841 GCTCAAATCA TTCCTGGTAC AGGAAACAAG CTTCTGATGT CTTCTCCTAA TTGTGAGATA
 9901 TATTATCAAA GTCCTTTATC ACTTTGTATG GCCAAAAGGA AGTCTGTTTC CACACCTGTC
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10141 GGCACCAAAT ACGAAACACC CATAAAGAAA AAAGAACTGA ATTCTCCTCA GATGACTCCA
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11161 CAATTCTTCA TCCTTAAGTC AGCATGATTA TAAGAAAAAT AGAACCCTCA GTGTAACTCT
11221 AATTCCTTTT TACTATTCCA GTGTGATCTC TGAAATTAAA TTACTTCAAC TAAAAATTCA
11281 AATACTTTAA ATCAGAAGAT TTCATAGTTA ATTTATTTTT TTTTTCAACA AAATGGTCAT
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```
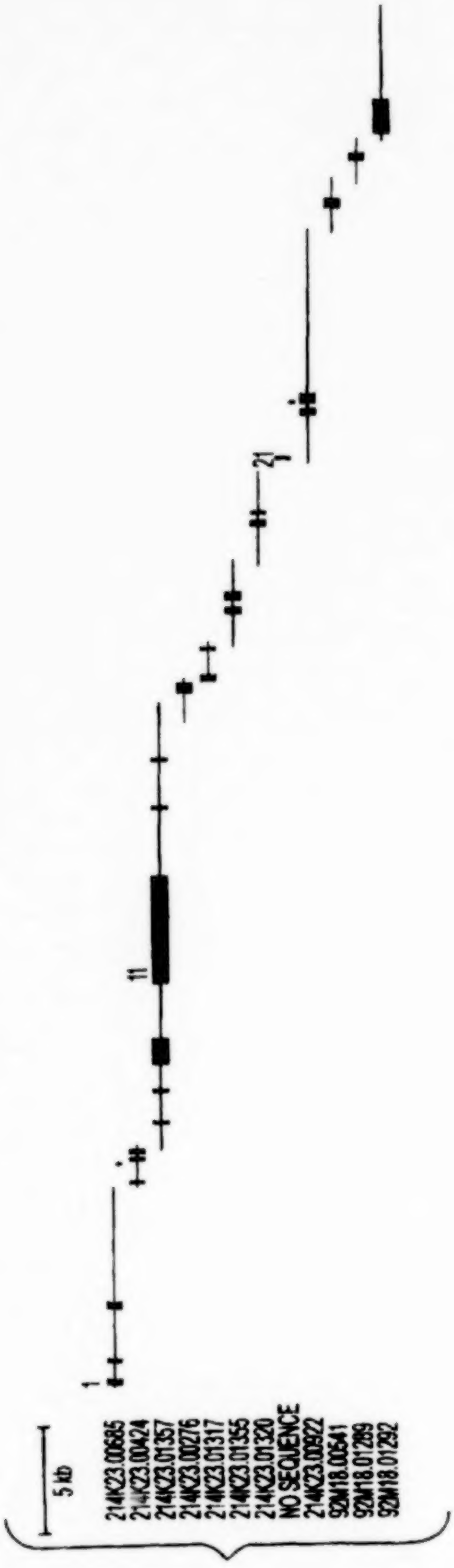

FIG. 3D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214K23.00424
214K23.01357
214K23.00276
214K23.01317
214K23.01355
214K23.01320
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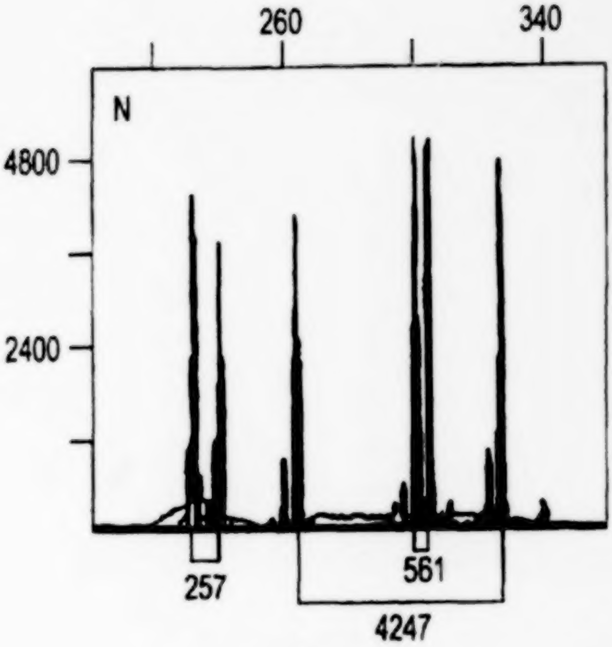
92M18.00541
92M18.01289
92M18.01292
1
11
21

FIG. 4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340
N
4800
2400
257
561
4247

FIG. 5A

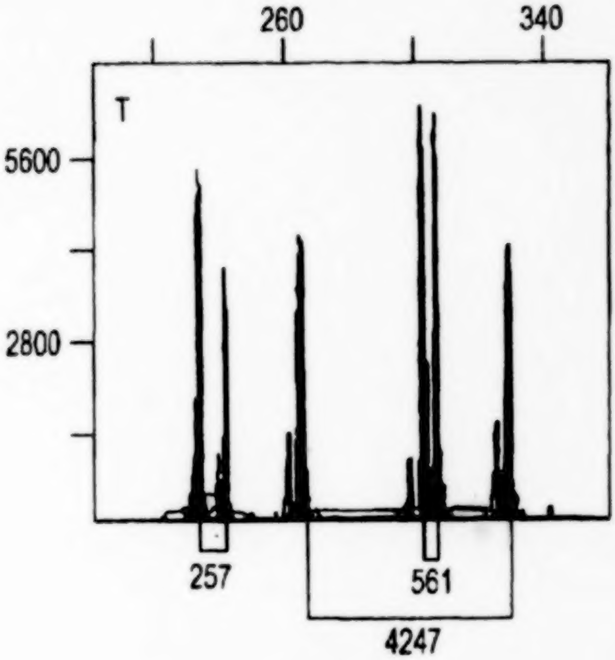
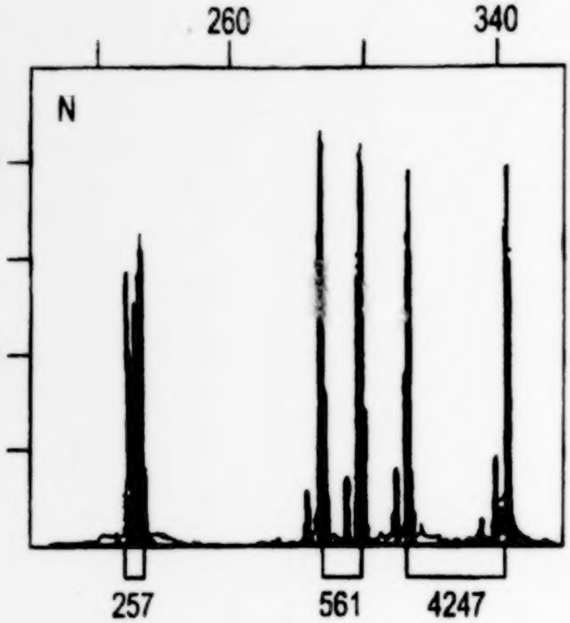

260
340
T
5600
2800
257
561
4247

FIG. 5B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5600
2800
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561
4247

FIG. 5C

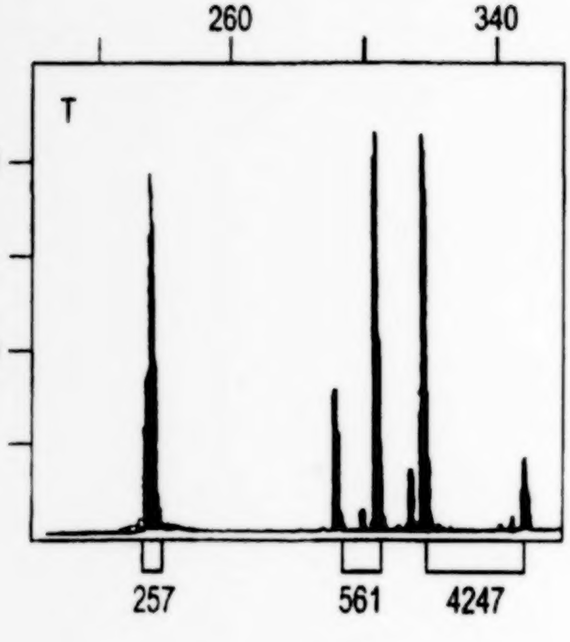
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FIG. 5D

CHROMOSOME 13-LINKED BREAST CANCER SUSCEPTIBILITY GENE

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of application Ser. No. 08/585,391, filed on 11 Jan. 1996, now abandoned, which is a continuation-in-part of application Ser. No. 08/576,559 filed on 21 Dec. 1995, now abandoned, which is a continuation-in-part of application Ser. No. 08/575,359, filed on 20 Dec. 1995, now abandoned, which is a continuation-in-part of application Ser. No. 08/573,779, filed on 18 Dec. 1995, now abandoned, all of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates generally to the field of human genetics. Specifically, the present invention relates to methods and materials used to isolate and detect a human cancer predisposing gene (BRCA2), some mutant alleles of which cause susceptibility to cancer, in particular, breast cancer in females and males. More specifically, the invention relates to germline mutations in the BRCA2 gene and their use in the diagnosis of predisposition to breast cancer. The present invention further relates to somatic mutations in the BRCA2 gene in human breast cancer and their use in the diagnosis and prognosis of human breast cancer. Additionally, the invention relates to somatic mutations in the BRCA2 gene in other human cancers and their use in the diagnosis and prognosis of human cancers. The invention also relates to the therapy of human cancers which have a mutation in the BRCA2 gene, including gene therapy, protein replacement therapy and protein mimetics. The invention further relates to the screening of drugs for cancer therapy. Finally, the invention relates to the screening of the BRCA2 gene for mutations, which are useful for diagnosing the predisposition to breast cancer.

The publications and other materials used herein to illuminate the background of the invention, and in particular, cases to provide additional details respecting the practice, are incorporated herein by reference, and for convenience, are referenced by author and date in the following text and respectively grouped in the appended List of References.

BACKGROUND OF THE INVENTION

The genetics of cancer is complicated, involving multiple dominant, positive regulators of the transformed state (oncogenes) as well as multiple recessive, negative regulators (tumor suppressor genes). Over one hundred oncogenes have been characterized. Fewer than a dozen tumor suppressor genes have been identified, but the number is expected to increase beyond fifty (Knudson, 1993).

The involvement of so many genes underscores the complexity of the growth control mechanisms that operate in cells to maintain the integrity of normal tissue. This complexity is manifest in another way. So far, no single gene has been shown to participate in the development of all, or even the majority of human cancers. The most common oncogenic mutations are in the H-ras gene, found in 10–15% of all solid tumors (Anderson et al., 1992). The most frequently mutated tumor suppressor genes are the TP53 gene, homozygously deleted in roughly 50% of all tumors, and CDKN2, which was homozygously deleted in 46% of tumor cell lines examined (Kamb et al., 1994a). Without a target that is common to all transformed cells, the dream of a "magic bullet" that can destroy or revert cancer cells while leaving normal tissue unharmed is improbable. The hope for a new generation of specifically targeted antitumor drugs may rest on the ability to identify tumor suppressor genes or oncogenes that play general roles in control of cell division.

The tumor suppressor genes which have been cloned and characterized influence susceptibility to: 1) Retinoblastoma (RB1); 2) Wilms' tumor (WT1); 3) Li-Fraumeni (TP53); 4) Familial adenomatous polyposis (APC); 5) Neurofibromatosis type 1 (NF 1); 6) Neurofibromatosis type 2 (NF2); 7) von Hippel-Lindau syndrome (VHL); 8) Multiple endocrine neoplasia type 2A (MEN2A); and 9) Melanoma (CDKN2).

Tumor suppressor loci that have been mapped genetically but not yet isolated include genes for: Multiple endocrine neoplasia type 1 (MEN1); Lynch cancer family syndrome 2 (LCFS2); Neuroblastoma (NB); Basal cell nevus syndrome (BCNS); Beckwith-Wiedemann syndrome (BWS); Renal cell carcinoma (RCC); Tuberous sclerosis 1 (TSC1); and Tuberous sclerosis 2 (TSC2). The tumor suppressor genes that have been characterized to date encode products with similarities to a variety of protein types, including DNA binding proteins (WT1), ancillary transcription regulators (RB 1), GTPase activating proteins or GAPs (NF1), cytoskeletal components (NF2), membrane bound receptor kinases (MEN2A), cell cycle regulators (CDKN2) and others with no obvious similarity to known proteins (APC and VHL).

In many cases, the tumor suppressor gene originally identified through genetic studies has been shown to be lost or mutated in some sporadic tumors. This result suggests that regions of chromosomal aberration may signify the position of important tumor suppressor genes involved both in genetic predisposition to cancer and in sporadic cancer.

One of the hallmarks of several tumor suppressor genes characterized to date is that they are deleted at high frequency in certain tumor types. The deletions often involve loss of a single allele, a so-called loss of heterozygosity (LOH), but may also involve homozygous deletion of both alleles. For LOH, the remaining allele is presumed to be nonfunctional, either because of a preexisting inherited mutation, or because of a secondary sporadic mutation.

Breast cancer is one of the most significant diseases that affects women. At the current rate, American women have a 1 in 8 risk of developing breast cancer by age 95 (American Cancer Society, 1992). Treatment of breast cancer at later stages is often futile and disfiguring, making early detection a high priority in medical management of the disease. Ovarian cancer, although less frequent than breast cancer, is often rapidly fatal and is the fourth most common cause of cancer mortality in American women. Genetic factors contribute to an ill-defined proportion of breast cancer incidence, estimated to be about 5% of all cases but approximately 25% of cases diagnosed before age 40 (Claus et al., 1991). Breast cancer has been subdivided into two types, early-age onset and late-age onset, based on an inflection in the age-specific incidence curve around age 50. Mutation of one gene, BRCA1, is thought to account for approximately 45% of familial breast cancer, but at least 80% of families with both breast and ovarian cancer (Easton et al., 1993).

The BRCA1 gene has been isolated (Futreal et al., 1994; Miki et al., 1994) following an intense effort following its mapping in 1990 (Hall et al., 1990; Narod et al., 1991). A second locus, BRCA2, has recently been mapped to chromosome 13 (Wooster et al., 1994) and appears to account for a proportion of early-onset breast cancer roughly equal to BRCA1, but confers a lower risk of ovarian cancer. The remaining susceptibility to early-onset breast cancer is divided between as-yet unmapped genes for familial cancer, and rarer germline mutations in genes such as TP53 (Malkin et al., 1990). It has also been suggested that heterozygote carriers for defective forms of the Ataxia-Telangiectasia gene are at higher risk for breast cancer (Swift et al., 1976; Swift et al., 1991). Late-age onset breast cancer is also often familial although the risks in relatives are not as high as those for early-onset breast cancer (Cannon-Albright et al., 1994; Mettlin et al., 1990). However, the percentage of such cases due to genetic susceptibility is unknown.

Breast cancer has long been recognized to be, in part, a familial disease (Anderson, 1972). Numerous investigators have examined the evidence for genetic inheritance and concluded that the data are most consistent with dominant inheritance for a major susceptibility locus or loci (Bishop and Gardner, 1980; Go et al., 1983; Williams and Anderson, 1984; Bishop et al., 1988; Newman et al., 1988; Claus et al., 1991). Recent results demonstrate that at least three loci exist which convey susceptibility to breast cancer as well as other cancers. These loci are the TP53 locus on chromosome 17p (Malkin et al., 1990), a 17q-linked susceptibility locus known as BRCA1 (Hall et al., 1990), and one or more loci responsible for the unmapped residual. Hall et al. (1990) indicated that the inherited breast cancer susceptibility in kindreds with early age onset is linked to chromosome 17q21; although subsequent studies by this group using a more appropriate genetic model partially refuted the limitation to early onset breast cancer (Margaritte et al., 1992).

Most strategies for cloning the chromosome 13-linked breast cancer predisposing gene (BRCA2) require precise genetic localization studies. The simplest model for the functional role of BRCA2 holds that alleles of BRCA2 that predispose to cancer are recessive to wild type alleles; that is, cells that contain at least one wild type BRCA2 allele are not cancerous. However, cells that contain one wild type BRCA2 allele and one predisposing allele may occasionally suffer loss of the wild type allele either by random mutation or by chromosome loss during cell division (nondisjunction). All the progeny of such a mutant cell lack the wild type function of BRCA2 and may develop into tumors. According to this model, predisposing alleles of BRCA2 are recessive, yet susceptibility to cancer is inherited in a dominant fashion: women who possess one predisposing allele (and one wild type allele) risk developing cancer, because their mammary epithelial cells may spontaneously lose the wild type BRCA2 allele. This model applies to a group of cancer susceptibility loci known as tumor suppressors or antioncogenes, a class of genes that includes the retinoblastoma gene and neurofibromatosis gene. By inference this model may explain the BRCA1 function, as has recently been suggested (Smith et al., 1992).

A second possibility is that BRCA2 predisposing alleles are truly dominant; that is, a wild type allele of BRCA2 cannot overcome the tumor forming role of the predisposing allele. Thus, a cell that carries both wild type and mutant alleles would not necessarily lose the wild type copy of BRCA2 before giving rise to malignant cells. Instead, mammary cells in predisposed individuals would undergo some other stochastic change(s) leading to cancer.

If BRCA2 predisposing alleles are recessive, the BRCA2 gene is expected to be expressed in normal mammary tissue but not functionally expressed in mammary tumors. In contrast, if BRCA2 predisposing alleles are dominant, the wild type BRCA2 gene may or may not be expressed in normal mammary tissue. However, the predisposing allele will likely be expressed in breast tumor cells.

The chromosome 13 linkage of BRCA2 was independently confirmed by studying fifteen families that had multiple cases of early-onset breast cancer cases that were not linked to BRCA1 (Wooster et al., 1994). These studies claimed to localize the gene within a large region, 6 centiMorgans (cM), or approximately 6 million base pairs, between the markers D13S289 and D13S267, placing BRCA2 in a physical region defined by 13q12—13. The size of these regions and the uncertainty associated with them has made it difficult to design and implement physical mapping and/or cloning strategies for isolating the BRCA2 gene. Like BRCA1, BRCA2 appears to confer a high risk of early-onset breast cancer in females. However, BRCA2 does not appear to confer a substantially elevated risk of ovarian cancer, although it does appear to confer an elevated risk of male breast cancer (Wooster, et al., 1994).

Identification of a breast cancer susceptibility locus would permit the early detection of susceptible individuals and greatly increase our ability to understand the initial steps which lead to cancer. As susceptibility loci are often altered during tumor progression, cloning these genes could also be important in the development of better diagnostic and prognostic products, as well as better cancer therapies.

SUMMARY OF THE INVENTION

The present invention relates generally to the field of human genetics. Specifically, the present invention relates to methods and materials used to isolate and detect a human breast cancer predisposing gene (BRCA2), some alleles of which cause susceptibility to cancer, in particular breast cancer in females and males. More specifically, the present invention relates to germline mutations in the BRCA2 gene and their use in the diagnosis of predisposition to breast cancer. The invention further relates to somatic mutations in the BRCA2 gene in human breast cancer and their use in the diagnosis and prognosis of human breast cancer. Additionally, the invention relates to somatic mutations in the BRCA2 gene in other human cancers and their use in the diagnosis and prognosis of human cancers. The invention also relates to the therapy of human cancers which have a mutation in the BRCA2 gene, including gene therapy, protein replacement therapy and protein mimetics. The invention further relates to the screening of drugs for cancer therapy. Finally, the invention relates to the screening of the BRCA2 gene for mutations, which are useful for diagnosing the predisposition to breast cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a schematic map of STSs, P1s, BACs and YACs in the BRCA2 region.

FIG. 2 shows the sequence-space relationship between the cDNA clones, hybrid selected clones, cDNA PCR products and genomic sequences used to assemble the BRCA2 transcript sequence. 2-Br-C:RACE is a biotin-capture RACE product obtained from both human breast and human thymus cDNA. The cDNA clone λ. sC713.1 was identified by screening a pool of human testis and HepG2 cDNA libraries with hybrid selected clone GT 713. The sequence 1-BR:CG026→5kb was generated from a PCR product beginning at the exon 7/8 junction (within λ. sC713.1) and terminating within an hybrid selected clone that is part of exon 11. The sequence of exon 11 was corrected by comparison to hybrid selected clones, genomic sequence in the public domain and radioactive DNA sequencing gels. Hybrid selected clones located within that exon (clone names beginning with nH or GT) are placed below it. The cDNA clones λ. wCBF1B8.1, λ. wCBF1A5.1, λ. wCBF1A5.12, λ. wCBF1B6.2 and λ. wCBF1B6.3 were identified by screening a pool of human mammary gland, placenta, testis and HepG2 cDNA libraries with the exon trapped clones wXBF1B8, wXPF1A5 and wXBF1B6. The clone λ. wCBF1B6.3 is chimeric (indicated by the dashed line), but its 5' end contained an important overlap with λ. wCBF11A5.1. denotes the translation initiator. denotes the translation terminator.

FIGS. 3A–3D show the DNA sequence of the BRCA2 gene (which is also set forth in SEQ ID NO: 1).

FIG. 4 shows the genomic organization of the BRCA2 gene. The exons (boxes and/or vertical lines) are parsed across the genomic sequences (ftp://genome.wustl.edu/pub/gsc1/brca;) (horizontal lines) such that their sizes and spacing are proportional. The name of each genomic sequence is given at the left side of the figure. The sequences 92M18.00541 and 92M18.01289 actually overlap. Distances between the other genomic sequences are not known. Neither the public database nor our sequence database contained genomic sequences overlapping with exon 21. Exons 1, 11 and 21 are numbered. "*" denotes two adjacent exons spaced closely enough that they are not resolved at this scale.

FIGS. 5A–5D show a loss of heterozygosity (LOH) analysis of primary breast tumors. Alleles of STR markers are indicated below the chromatogram. Shown are one example of a tumor heterozygous at BRCA2 (FIGS. 5A and 5B) and an example of a tumor with LOH at BRCA2 (FIGS. 5C and 5D). Fluorescence units are on the ordinate; size in basepairs is on the abscissa. N is for normal (FIGS. 5A and 5C) and T is for tumor (FIGS. 5B and 5D).

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates generally to the field of human genetics. Specifically, the present invention relates to methods and materials used to isolate and detect a human breast cancer predisposing gene (BRCA2), some alleles of which cause susceptibility to cancer, in particular breast cancer in females and males. More specifically, the present invention relates to germline mutations in the BRCA2 gene and their use in the diagnosis of predisposition to breast cancer. The invention further relates to somatic mutations in the BRCA2 gene in human breast cancer and their use in the diagnosis and prognosis of human breast cancer. Additionally, the invention relates to somatic mutations in the BRCA2 gene in other human cancers and their use in the diagnosis and prognosis of human cancers. The invention also relates to the therapy of human cancers which have a mutation in the BRCA2 gene, including gene therapy, protein replacement therapy and protein mimetics. The invention further relates to the screening of drugs for cancer therapy. Finally, the invention relates to the screening of the BRCA2 gene for mutations, which are useful for diagnosing the predisposition to breast cancer.

The present invention provides an isolated polynucleotide comprising all, or a portion of the BRCA2 locus or of a mutated BRCA2 locus, preferably at least eight bases and not more than about 100 kb in length. Such polynucleotides may be antisense polynucleotides. The present invention also provides a recombinant construct comprising such an isolated polynucleotide, for example, a recombinant construct suitable for expression in a transformed host cell.

Also provided by the present invention are methods of detecting a polynucleotide comprising a portion of the BRCA2 locus or its expression product in an analyte. Such methods may further comprise the step of amplifying the portion of the BRCA2 locus, and may further include a step of providing a set of polynucleotides which are primers for amplification of said portion of the BRCA2 locus. The method is useful for either diagnosis of the predisposition to cancer or the diagnosis or prognosis of cancer.

The present invention also provides isolated antibodies, preferably monoclonal antibodies, which specifically bind to an isolated polypeptide comprised of at least five amino acid residues encoded by the BRCA2 locus.

The present invention also provides kits for detecting in an analyte a polynucleotide comprising a portion of the BRCA2 locus, the kits comprising a polynucleotide complementary to the portion of the BRCA2 locus packaged in a suitable container, and instructions for its use.

The present invention further provides methods of preparing a polynucleotide comprising polymerizing nucleotides to yield a sequence comprised of at least eight consecutive nucleotides of the BRCA2 locus; and methods of preparing a polypeptide comprising polymerizing amino acids to yield a sequence comprising at least five amino acids encoded within the BRCA2 locus.

The present invention further provides methods of screening the BRCA2 gene to identify mutations. Such methods may further comprise the step of amplifying a portion of the BRCA2 locus, and may further include a step of providing a set of polynucleotides which are primers for amplification of said portion of the BRCA2 locus. The method is useful for identifying mutations for use in either diagnosis of the predisposition to cancer or the diagnosis or prognosis of cancer.

The present invention further provides methods of screening suspected BRCA2 mutant alleles to identify mutations in the BRCA2 gene.

In addition, the present invention provides methods of screening drugs for cancer therapy to identify suitable drugs for restoring BRCA2 gene product function.

Finally, the present invention provides the means necessary for production of gene-based therapies directed at cancer cells. These therapeutic agents may take the form of polynucleotides comprising all or a portion of the BRCA2 locus placed in appropriate vectors or delivered to target cells in more direct ways such that the function of the BRCA2 protein is reconstituted. Therapeutic agents may also take the form of polypeptides based on either a portion of, or the entire protein sequence of BRCA2. These may functionally replace the activity of BRCA2 in vivo.

It is a discovery of the present invention that the BRCA2 locus which predisposes individuals to breast cancer, is a gene encoding a BRCA2 protein. This gene is termed BRCA2 herein. It is a discovery of the present invention that mutations in the BRCA2 locus in the germline are indicative of a predisposition to breast cancer in both men and women. Finally, it is a discovery of the present invention that somatic mutations in the BRCA2 locus are also associated with breast cancer and other cancers, which represents an indicator of these cancers or of the prognosis of these cancers. The mutational events of the BRCA2 locus can involve deletions, insertions and point mutations within the coding sequence and the non-coding sequence.

Starting from a region on human chromosome 13 of the human genome, which has a size estimated at about 6 million base pairs, a smaller region of 1 to 1.5 million bases which contains a genetic locus, BRCA2, which causes susceptibility to cancer, including breast cancer, has been identified.

The region containing the BRCA2 locus was identified using a variety of genetic techniques. Genetic mapping techniques initially defined the BRCA2 region in terms of recombination with genetic markers. Based upon studies of large extended families ("kindreds") with multiple cases of breast cancer, a chromosomal region has been pinpointed that contains the BRCA2 gene. A region which contains the BRCA2 locus is physically bounded by the markers D13S289 and D13S267.

The use of the genetic markers provided by this invention allowed the identification of clones which cover the region from a human yeast artificial chromosome (YAC) or a human bacterial artificial chromosome (BAC) library. It also allowed for the identification and preparation of more easily manipulated P1 and BAC clones from this region and the construction of a contig from a subset of the clones. These P1s, YACs and BACs provide the basis for cloning the BRCA2 locus and provide the basis for developing reagents effective, for example, in the diagnosis and treatment of breast and/or ovarian cancer. The BRCA2 gene and other potential susceptibility genes have been isolated from this region. The isolation was done using software trapping (a computational method for identifying sequences likely to contain coding exons, from contiguous or discontinuous genomic DNA sequences), hybrid selection techniques and direct screening, with whole or partial cDNA inserts from P1s and BACs, in the region to screen cDNA libraries. These methods were used to obtain sequences of loci expressed in breast and other tissue. These candidate loci were analyzed to identify sequences which confer cancer susceptibility. We have discovered that there are mutations in the coding sequence of the BRCA2 locus in kindreds which are responsible for the chromosome 13-linked cancer susceptibility known as BRCA2. The present invention not only facilitates the early detection of certain cancers, so vital to patient survival, but also permits the detection of susceptible individuals before they develop cancer.

Population Resources

Large, well-documented Utah kindreds are especially important in providing good resources for human genetic studies. Each large kindred independently provides the power to detect whether a BRCA2 susceptibility allele is segregating in that family. Recombinants informative for localization and isolation of the BRCA2 locus could be obtained only from kindreds large enough to confirm the presence of a susceptibility allele. Large sibships are especially important for studying breast cancer, since penetrance of the BRCA2 susceptibility allele is reduced both by age and sex, making informative sibships difficult to find. Furthermore, large sibships are essential for constructing haplotypes of deceased individuals by inference from the haplotypes of their close relatives.

While other populations may also provide beneficial information, such studies generally require much greater effort, and the families are usually much smaller and thus less informative.

Utah's age-adjusted breast cancer incidence is 20% lower than the average U.S. rate. The lower incidence in Utah is probably due largely to an early age at first pregnancy, increasing the probability that cases found in Utah kindreds carry a genetic predisposition.

Genetic Mapping

Given a set of informative families, genetic markers are essential for linking a disease to a region of a chromosome. Such markers include restriction fragment length polymorphisms (RFLPs) (Botstein et al., 1980), markers with a variable number of tandem repeats (VNTRs) (Jeffreys et al., 1985; Nakamura et al., 1987), and an abundant class of DNA polymorphisms based on short tandem repeats (STRs), especially repeats of CpA (Weber and May, 1989; Litt et al., 1989). To generate a genetic map, one selects potential genetic markers and tests them using DNA extracted from members of the kindreds being studied.

Genetic markers useful in searching for a genetic locus associated with a disease can be selected on an ad hoc basis, by densely covering a specific chromosome, or by detailed analysis of a specific region of a chromosome. A preferred method for selecting genetic markers linked with a disease involves evaluating the degree of informativeness of kindreds to determine the ideal distance between genetic markers of a given degree of polymorphism, then selecting markers from known genetic maps which are ideally spaced for maximal efficiency. Informativeness of kindreds is measured by the probability that the markers will be heterozygous in unrelated individuals. It is also most efficient to use STR markers which are detected by amplification of the target nucleic acid sequence using PCR; such markers are highly informative, easy to assay (Weber and May, 1989), and can be assayed simultaneously using multiplexing strategies (Skolnick and Wallace, 1988), greatly reducing the number of experiments required.

Once linkage has been established, one needs to find markers that flank the disease locus, i.e., one or more markers proximal to the disease locus, and one or more markers distal to the disease locus. Where possible, candidate markers can be selected from a known genetic map. Where none is known, new markers can be identified by the STR technique, as shown in the Examples.

Genetic mapping is usually an iterative process. In the present invention, it began by defining flanking genetic markers around the BRCA2 locus, then replacing these flanking markers with other markers that were successively closer to the BRCA2 locus. As an initial step, recombination events, defined by large extended kindreds, helped specifically to localize the BRCA2 locus as either distal or proximal to a specific genetic marker (Wooster et al., 1994).

The region surrounding BRCA2, until the disclosure of the present invention, was not well mapped and there were few markers. Therefore, short repetitive sequences were developed from cosmids, P1s, BACs and YACs, which physically map to the region and were analyzed in order to develop new genetic markers. Novel STRs were found which were both polymorphic and which mapped to the BRCA2 region.

Physical Mapping

Three distinct methods were employed to physically map the region. The first was the use of yeast artificial chromosomes (YACs) to clone the BRCA2 region. The second was the creation of a set of P1, BAC and cosmid clones which cover the region containing the BRCA2 locus.

Yeast Artificial Chromosomes (YACs). Once a sufficiently small region containing the BRCA2 locus was identified, physical isolation of the DNA in the region proceeded by identifying a set of overlapping YACs which covers the region. Useful YACs can be isolated from known libraries, such as the St. Louis and CEPH YAC libraries, which are widely distributed and contain approximately 50,000 YACs each. The YACs isolated were from these publicly accessible libraries and can be obtained from a number of sources including the Michigan Genome Center. Clearly, others who had access to these YACs, without the disclosure of the present invention, would not have known the value of the specific YACs we selected since they would not have known which YACs were within, and which YACs outside of, the smallest region containing the BRCA2 locus.

P1 and BAC Clones. In the present invention, it is advantageous to proceed by obtaining P1 and BAC clones to cover this region. The smaller size of these inserts, compared to YAC inserts, makes them more useful as specific hybridization probes. Furthermore, having the cloned DNA in bacterial cells, rather than in yeast cells, greatly increases the ease with which the DNA of interest can be manipulated, and improves the signal-to-noise ratio of hybridization assays.

P1 and BAC clones are obtained by screening libraries constructed from the total human genome with specific sequence tagged sites (STSs) derived from the YACs, P1s and BACs, isolated as described herein.

These P1 and BAC clones can be compared by interspersed repetitive sequence (IRS) PCR and/or restriction enzyme digests followed by gel electrophoresis and comparison of the resulting DNA fragments ("fingerprints") (Maniatis et al., 1982). The clones can also be characterized by the presence of STSs. The fingerprints are used to define an overlapping contiguous set of clones which covers the region but is not excessively redundant, referred to herein as a "minimum tiling path". Such a minimum tiling path forms the basis for subsequent experiments to identify cDNAs which may originate from the BRCA2 locus.

P1 clones (Sternberg, 1990; Sternberg et al., 1990; Pierce et al., 1992; Shizuya et al., 1992) were isolated by Genome Sciences using PCR primers provided by us for screening. BACs were provided by hybridization techniques in Dr. Mel Simon's laboratory and by analysis of PCR pools in our laboratory. The strategy of using P1 and BAC clones also permitted the covering of the genomic region with an independent set of clones not derived from YACs. This guards against the possibility of deletions in YACs. These new sequences derived from the P1 and BAC clones provide the material for further screening for candidate genes, as described below.

Gene Isolation

There are many techniques for testing genomic clones for the presence of sequences likely to be candidates for the coding sequence of a locus one is attempting to isolate, including but not limited to: (a) zoo blots, (b) identifying HTF islands, (c) exon trapping, (d) hybridizing cDNA to P1s, BAC or YACs and (e) screening cDNA libraries.

(a) Zoo blots. The first technique is to hybridize cosmids to Southern blots to identify DNA sequences which are evolutionarily conserved, and which therefore give positive hybridization signals with DNA from species of varying degrees of relationship to humans (such as monkey, cow, chicken, pig, mouse and rat). Southern blots containing such DNA from a variety of species are commercially available (Clonetech, Cat. 7753–1).

(b) Identifying HTF islands. The second technique involves finding regions rich in the nucleotides C and G, which often occur near or within coding sequences. Such sequences are called HTF (HpaI tiny fragment) or CpG islands, as restriction enzymes specific for sites which contain CpG dimers cut frequently in these regions (Lindsay et al., 1987).

(c) Exon trapping. The third technique is exon trapping, a method that identifies sequences in genomic DNA which contain splice junctions and therefore are likely to comprise coding sequences of genes. Exon amplification (Buckler et al., 1991) is used to select and amplify exons from DNA clones described above. Exon amplification is based on the selection of RNA sequences which are flanked by functional 5' and/or 3' splice sites. The products of the exon amplification are used to screen the breast cDNA libraries to identify a manageable number of candidate genes for further study. Exon trapping can also be performed on small segments of sequenced DNA using computer programs or by software trapping.

(d) Hybridizing cDNA to P1s, BACs or YACs. The fourth technique is a modification of the selective enrichment technique which utilizes hybridization of cDNA to cosmids, P1s, BACs or YACs and permits transcribed sequences to be identified in, and recovered from cloned genomic DNA (Kandpal et al., 1990). The selective enrichment technique, as modified for the present purpose, involves binding DNA from the region of BRCA2 present in a YAC to a column matrix and selecting cDNAs from the relevant libraries which hybridize with the bound DNA, followed by amplification and purification of the bound DNA, resulting in a great enrichment for cDNAs in the region represented by the cloned genomic DNA.

(e) Identification of cDNAs. The fifth technique is to identify cDNAs that correspond to the BRCA2 locus. Hybridization probes containing putative coding sequences, selected using any of the above techniques, are used to screen various libraries, including breast tissue cDNA libraries and any other necessary libraries.

Another variation on the theme of direct selection of cDNA can be used to find candidate genes for BRCA2 (Lovett et al., 1991; Futreal, 1993). This method uses cosmid, P1 or BAC DNA as the probe. The probe DNA is digested with a blunt cutting restriction enzyme such as HaeIII. Double stranded adapters are then ligated onto the DNA and serve as binding sites for primers in subsequent PCR amplification reactions using biotinylated primers. Target cDNA is generated from mRNA derived from tissue samples, e.g., breast tissue, by synthesis of either random primed or oligo(dT) primed first strand followed by second strand synthesis. The cDNA ends are rendered blunt and ligated onto double-stranded adapters. These adapters serve as amplification sites for PCR. The target and probe sequences are denatured and mixed with human C_0t-1 DNA to block repetitive sequences. Solution hybridization is carried out to high C_0t-½ values to ensure hybridization of rare target cDNA molecules. The annealed material is then captured on avidin beads, washed at high stringency and the retained cDNAs are eluted and amplified by PCR. The selected cDNA is subjected to further rounds of enrichment before cloning into a plasmid vector for analysis.

Testing the cDNA for Candidacy

Proof that the cDNA is the BRCA2 locus is obtained by finding sequences in DNA extracted from affected kindred members which create abnormal BRCA2 gene products or abnormal levels of BRCA2 gene product. Such BRCA2susceptibility alleles will co-segregate with the disease in large kindreds. They will also be present at a much higher frequency in non-kindred individuals with breast cancer then in individuals in the general population. Finally, since tumors often mutate somatically at loci which are in other instances mutated in the germline, we expect to see normal germline BRCA2 alleles mutated into sequences which are identical or similar to BRCA2 susceptibility alleles in DNA extracted from tumor tissue. Whether one is comparing BRCA2 sequences from tumor tissue to BRCA2 alleles from the germline of the same individuals, or one is comparing germline BRCA2 alleles from cancer cases to those from unaffected individuals, the key is to find mutations which are serious enough to cause obvious disruption to the normal function of the gene product. These mutations can take a number of forms. The most severe forms would be frame shift mutations or large deletions which would cause the gene to code for an abnormal protein or one which would significantly alter protein expression. Less severe disruptive mutations would include small in-frame deletions and nonconservative base pair substitutions which would have a significant effect on the protein produced, such as changes to or from a cysteine residue, from a basic to an acidic amino acid or vice versa, from a hydrophobic to hydrophilic amino acid or vice versa, or other mutations which would affect secondary, tertiary or quaternary protein structure. Silent mutations or those resulting in conservative amino acid substitutions would not generally be expected to disrupt protein function.

According to the diagnostic and prognostic method of the present invention, alteration of the wild-type BRCA2 locus is detected. In addition, the method can be performed by detecting the wild-type BRCA2 locus and confirming the lack of a predisposition to cancer at the BRCA2 locus. "Alteration of a wild-type gene" encompasses all forms of mutations including deletions, insertions and point mutations in the coding and noncoding regions. Deletions may be of the entire gene or of only a portion of the gene. Point mutations may result in stop codons, frameshift mutations or amino acid substitutions. Somatic mutations are those which occur only in certain tissues, e.g., in the tumor tissue, and are not inherited in the germline. Germline mutations can be found in any of a body's tissues and are inherited. If only a single allele is somatically mutated, an early neoplastic state is indicated. However, if both alleles are somatically mutated, then a late neoplastic state is indicated. The finding of BRCA2 mutations thus provides both diagnostic and prognostic information. A BRCA2 allele which is not deleted (e.g., found on the sister chromosome to a chromosome carrying a BRCA2 deletion) can be screened for other mutations, such as insertions, small deletions, and point mutations. It is believed that many mutations found in tumor tissues will be those leading to decreased expression of the BRCA2 gene product. However, mutations leading to nonfunctional gene products would also lead to a cancerous state. Point mutational events may occur in regulatory regions, such as in the promoter of the gene, leading to loss or diminution of expression of the mRNA. Point mutations may also abolish proper RNA processing, leading to loss of expression of the BRCA2 gene product, or to a decrease in mRNA stability or translation efficiency.

Useful diagnostic techniques include, but are not limited to fluorescent in situ hybridization (FISH), direct DNA sequencing, PFGE analysis, Southern blot analysis, single stranded conformation analysis (SSCA), RNase protection assay, allele-specific oligonucleotide (ASO), dot blot analysis and PCR-SSCP, as discussed in detail further below.

Predisposition to cancers, such as breast cancer, and the other cancers identified herein, can be ascertained by testing any tissue of a human for mutations of the BRCA2 gene. For example, a person who has inherited a germline BRCA2 mutation would be prone to develop cancers. This can be determined by testing DNA from any tissue of the person's body. Most simply, blood can be drawn and DNA extracted from the cells of the blood. In addition, prenatal diagnosis can be accomplished by testing fetal cells, placental cells or amniotic cells for mutations of the BRCA2 gene. Alteration of a wild-type BRCA2 allele, whether, for example, by point mutation or deletion, can be detected by any of the means discussed herein.

There are several methods that can be used to detect DNA sequence variation. Direct DNA sequencing, either manual sequencing or automated fluorescent sequencing can detect sequence variation. For a gene as large as BRCA2, manual sequencing is very labor-intensive, but under optimal conditions, mutations in the coding sequence of a gene are rarely missed. Another approach is the single-stranded conformation polymorphism assay (SSCA) (Orita et al., 1989). This method does not detect all sequence changes, especially if the DNA fragment size is greater than 200 bp, but can be optimized to detect most DNA sequence variation. The reduced detection sensitivity is a disadvantage, but the increased throughput possible with SSCA makes it an attractive, viable alternative to direct sequencing for mutation detection on a research basis. The fragments which have shifted mobility on SSCA gels are then sequenced to determine the exact nature of the DNA sequence variation. Other approaches based on the detection of mismatches between the two complementary DNA strands include clamped denaturing gel electrophoresis (CDGE) (Sheffield et al., 1991), heteroduplex analysis (HA) (White et al., 1992) and chemical mismatch cleavage (CMC) (Grompe et al., 1989). None of the methods described above will detect large deletions, duplications or insertions, nor will they detect a regulatory mutation which affects transcription or translation of the protein. Other methods which might detect these classes of mutations such as a protein truncation assay or the asymmetric assay, detect only specific types of mutations and would not detect missense mutations. A review of currently available methods of detecting DNA sequence variation can be found in a recent review by Grompe (1993). Once a mutation is known, an allele specific detection approach such as allele specific oligonucleotide (ASO) hybridization can be utilized to rapidly screen large numbers of other samples for that same mutation.

In order to detect the alteration of the wild-type BRCA2 gene in a tissue, it is helpful to isolate the tissue free from surrounding normal tissues. Means for enriching tissue preparation for tumor cells are known in the art. For example, the tissue may be isolated from paraffin or cryostat sections. Cancer cells may also be separated from normal cells by flow cytometry. These techniques, as well as other techniques for separating tumor cells from normal cells, are well known in the art. If the tumor tissue is highly contaminated with normal cells, detection of mutations is more difficult.

A rapid preliminary analysis to detect polymorphisms in DNA sequences can be performed by looking at a series of Southern blots of DNA cut with one or more restriction enzymes, preferably with a large number of restriction enzymes. Each blot contains a series of normal individuals and a series of cancer cases, tumors, or both. Southern blots displaying hybridizing fragments (differing in length from control DNA when probed with sequences near or including the BRCA2 locus) indicate a possible mutation. If restriction enzymes which produce very large restriction fragments are used, then pulsed field gel electrophoresis (PFGE) is employed.

Detection of point mutations may be accomplished by molecular cloning of the BRCA2 allele(s) and sequencing the allele(s) using techniques well known in the art. Alternatively, the gene sequences can be amplified directly from a genomic DNA preparation from the tumor tissue, using known techniques. The DNA sequence of the amplified sequences can then be determined.

There are six well known methods for a more complete, yet still indirect, test for confirming the presence of a susceptibility allele: 1) single stranded conformation analysis (SSCA) (Orita et al., 1989); 2) denaturing gradient gel electrophoresis (DGGE) (Wartell et al., 1990; Sheffield et al., 1989); 3) RNase protection assays (Finkelstein et al., 1990; Kinszler et al., 1991); 4) allele-specific oligonucleotides (ASOs) (Conner et al., 1983); 5) the use of proteins which recognize nucleotide mismatches, such as the E. coli mutS protein (Modrich, 1991); and 6) allele-specific PCR (Rano & Kidd, 1989). For allele-specific PCR, primers are used which hybridize at their 3' ends to a particular BRCA2 mutation. If the particular BRCA2 mutation is not present, an amplification product is not observed. Amplification Refractory Mutation System (ARMS) can also be used, as disclosed in European Patent Application Publication No. 0332435 and in Newton et al., 1989. Insertions and deletions of genes can also be detected by cloning, sequencing and amplification. In addition, restriction fragment length polymorphism (RFLP) probes for the gene or surrounding marker genes can be used to score alteration of an allele or an insertion in a polymorphic fragment.

Such a method is particularly useful for screening relatives of an affected individual for the presence of the BRCA2 mutation found in that individual. Other techniques for detecting insertions and deletions as known in the art can be used.

In the first three methods (SSCA, DGGE and RNase protection assay), a new electrophoretic band appears. SSCA detects a band which migrates differentially because the sequence change causes a difference in single-strand, intramolecular base pairing. RNase protection involves cleavage of the mutant polynucleotide into two or more smaller fragments. DGGE detects differences in migration rates of mutant sequences compared to wild-type sequences, using a denaturing gradient gel. In an allele-specific oligonucleotide assay, an oligonucleotide is designed which detects a specific sequence, and the assay is performed by detecting the presence or absence of a hybridization signal. In the mutS assay, the protein binds only to sequences that contain a nucleotide mismatch in a heteroduplex between mutant and wild-type sequences.

Mismatches according to the present invention, are hybridized nucleic acid duplexes in which the two strands are not 100% complementary. Lack of total homology may be due to deletions, insertions, inversions or substitutions. Mismatch detection can be used to detect point mutations in the gene or in its mRNA product. While these techniques are less sensitive than sequencing, they are simpler to perform on a large number of tumor samples. An example of a mismatch cleavage technique is the RNase protection method. In the practice of the present invention, the method involves the use of a labeled riboprobe which is complementary to the human wild-type BRCA2 gene coding sequence. The riboprobe and either mRNA or DNA isolated from the tumor tissue are annealed (hybridized) together and subsequently digested with the enzyme RNase A which is able to detect some mismatches in a duplex RNA structure. If a mismatch is detected by RNase A, it cleaves at the site of the mismatch. Thus, when the annealed RNA preparation is separated on an electrophoretic gel matrix, if a mismatch has been detected and cleaved by RNase A, an RNA product will be seen which is smaller than the full length duplex RNA for the riboprobe and the mRNA or DNA. The riboprobe need not be the full length of the BRCA2 mRNA or gene but can be a segment of either. If the riboprobe comprises only a segment of the BRCA2 mRNA or gene, it will be desirable to use a number of these probes to screen the whole mRNA sequence for mismatches.

In similar fashion, DNA probes can be used to detect mismatches, through enzymatic or chemical cleavage. See, e.g., Cotton et al., 1988; Shenk et al., 1975; Novack et al., 1986. Alternatively, mismatches can be detected by shifts in the electrophoretic mobility of mismatched duplexes relative to matched duplexes. See, e.g., Cariello, 1988. With either riboprobes or DNA probes, the cellular mRNA or DNA which might contain a mutation can be amplified using PCR (see below) before hybridization. Changes in DNA of the BRCA2 gene can also be detected using Southern hybridization, especially if the changes are gross rearrangements, such as deletions and insertions.

DNA sequences of the BRCA2 gene which have been amplified by use of PCR may also be screened using allele-specific probes. These probes are nucleic acid oligomers, each of which contains a region of the BRCA2 gene sequence harboring a known mutation. For example, one oligomer may be about 30 nucleotides in length, corresponding to a portion of the BRCA2 gene sequence. By use of a battery of such allele-specific probes, PCR amplification products can be screened to identify the presence of a previously identified mutation in the BRCA2 gene. Hybridization of allele-specific probes with amplified BRCA2sequences can be performed, for example, on a nylon filter. Hybridization to a particular probe under stringent hybridization conditions indicates the presence of the same mutation in the tumor tissue as in the allele-specific probe.

The most definitive test for mutations in a candidate locus is to directly compare genomic BRCA2sequences from cancer patients with those from a control population. Alternatively, one could sequence messenger RNA after amplification, e.g., by PCR, thereby eliminating the necessity of determining the exon structure of the candidate gene.

Mutations from cancer patients falling outside the coding region of BRCA2 can be detected by examining the non-coding regions, such as introns and regulatory sequences near or within the BRCA2 gene. An early indication that mutations in noncoding regions are important may come from Northern blot experiments that reveal messenger RNA molecules of abnormal size or abundance in cancer patients as compared to control individuals.

Alteration of BRCA2 mRNA expression can be detected by any techniques known in the art. These include Northern blot analysis, PCR amplification and RNase protection. Diminished mRNA expression indicates an alteration of the wild-type BRCA2 gene. Alteration of wild-type BRCA2 genes can also be detected by screening for alteration of wild-type BRCA2 protein. For example, monoclonal antibodies immunoreactive with BRCA2 can be used to screen a tissue. Lack of cognate antigen would indicate a BRCA2 mutation. Antibodies specific for products of mutant alleles could also be used to detect mutant BRCA2 gene product. Such immunological assays can be done in any convenient formats known in the art. These include Western blots, immunohistochemical assays and ELISA assays. Any means for detecting an altered BRCA2 protein can be used to detect alteration of wild-type BRCA2 genes. Functional assays, such as protein binding determinations, can be used. In addition, assays can be used which detect BRCA2 biochemical function. Finding a mutant BRCA2 gene product indicates alteration of a wild-type BRCA2 gene.

Mutant BRCA2 genes or gene products can also be detected in other human body samples, such as serum, stool, urine and sputum. The same techniques discussed above for detection of mutant BRCA2 genes or gene products in tissues can be applied to other body samples. Cancer cells are sloughed off from tumors and appear in such body samples. In addition, the BRCA2 gene product itself may be secreted into the extracellular space and found in these body samples even in the absence of cancer cells. By screening such body samples, a simple early diagnosis can be achieved for many types of cancers. In addition, the progress of chemotherapy or radiotherapy can be monitored more easily by testing such body samples for mutant BRCA2 genes or gene products.

The methods of diagnosis of the present invention are applicable to any tumor in which BRCA2 has a role in tumorigenesis. The diagnostic method of the present invention is useful for clinicians, so they can decide upon an appropriate course of treatment.

The primer pairs of the present invention are useful for determination of the nucleotide sequence of a particular BRCA2 allele using PCR. The pairs of single-stranded DNA primers can be annealed to sequences within or surrounding the BRCA2 gene on chromosome 13 in order to prime amplifying DNA synthesis of the BRCA2 gene itself. A complete set of these primers allows synthesis of all of the nucleotides of the BRCA2 gene coding sequences, i.e., the exons. The set of primers preferably allows synthesis of both intron and exon sequences. Allele-specific primers can also be used. Such primers anneal only to particular BRCA2 mutant alleles, and thus will only amplify a product in the presence of the mutant allele as a template.

In order to facilitate subsequent cloning of amplified sequences, primers may have restriction enzyme site sequences appended to their 5' ends. Thus, all nucleotides of the primers are derived from BRCA2sequences or sequences adjacent to BRCA2, except for the few nucleotides necessary to form a restriction enzyme site. Such enzymes and sites are well known in the art. The primers themselves can be synthesized using techniques which are well known in the art. Generally, the primers can be made using oligonucleotide synthesizing machines which are commercially available. Given the sequence of the BRCA2 open reading frame shown in SEQ ID NO:1 and in FIG. 3, design of particular primers, in addition to those disclosed below, is well within the skill of the art.

The nucleic acid probes provided by the present invention are useful for a number of purposes. They can be used in Southern hybridization to genomic DNA and in the RNase protection method for detecting point mutations already discussed above. The probes can be used to detect PCR amplification products. They may also be used to detect mismatches with the BRCA2 gene or mRNA using other techniques.

It has been discovered that individuals with the wild-type BRCA2 gene do not have cancer which results from the BRCA2 allele. However, mutations which interfere with the function of the BRCA2 protein are involved in the pathogenesis of cancer. Thus, the presence of an altered (or a mutant) BRCA2 gene which produces a protein having a loss of function, or altered function, directly correlates to an increased risk of cancer. In order to detect a BRCA2 gene mutation, a biological sample is prepared and analyzed for a difference between the sequence of the BRCA2 allele being analyzed and the sequence of the wild-type BRCA2 allele. Mutant BRCA2 alleles can be initially identified by any of the techniques described above. The mutant alleles are then sequenced to identify the specific mutation of the particular mutant allele. Alternatively, mutant BRCA2 alleles can be initially identified by identifying mutant (altered) BRCA2 proteins, using conventional techniques. The mutant alleles are then sequenced to identify the specific mutation for each allele. The mutations, especially those which lead to an altered function of the BRCA2 protein, are then used for the diagnostic and prognostic methods of the present invention.

Definitions

The present invention employs the following definitions:

"Amplification of Polynucleotides" utilizes methods such as the polymerase chain reaction (PCR), ligation amplification (or ligase chain reaction, LCR) and amplification methods based on the use of Q-beta replicase. These methods are well known and widely practiced in the art. See, e.g., U.S. Pat. Nos. 4,683,195 and 4,683,202 and Innis et al., 1990 (for PCR); and Wu et al., 1989a (for LCR). Reagents and hardware for conducting PCR are commercially available. Primers useful to amplify sequences from the BRCA2 region are preferably complementary to, and hybridize specifically to sequences in the BRCA2 region or in regions that flank a target region therein. BRCA2sequences generated by amplification may be sequenced directly. Alternatively, but less desirably, the amplified sequence(s) may be cloned prior to sequence analysis. A method for the direct cloning and sequence analysis of enzymatically amplified genomic segments has been described by Scharf, 1986.

"Analyte polynucleotide" and "analyte strand" refer to a single- or double-stranded polynucleotide which is suspected of containing a target sequence, and which may be present in a variety of types of samples, including biological samples.

"Antibodies." The present invention also provides polyclonal and/or monoclonal antibodies and fragments thereof, and immunologic binding equivalents thereof, which are capable of specifically binding to the BRCA2 polypeptides and fragments thereof or to polynucleotide sequences from the BRCA2 region, particularly from the BRCA2 locus or a portion thereof. The term "antibody" is used both to refer to a homogeneous molecular entity, or a mixture such as a serum product made up of a plurality of different molecular entities. Polypeptides may be prepared synthetically in a peptide synthesizer and coupled to a carrier molecule (e.g., keyhole limpet hemocyanin) and injected over several months into rabbits. Rabbit sera is tested for immunoreactivity to the BRCA2 polypeptide or fragment. Monoclonal antibodies may be made by injecting mice with the protein polypeptides, fusion proteins or fragments thereof. Monoclonal antibodies will be screened by ELISA and tested for specific immunoreactivity with BRCA2 polypeptide or fragments thereof. See, Harlow & Lane, 1988. These antibodies will be useful in assays as well as pharmaceuticals.

Once a sufficient quantity of desired polypeptide has been obtained, it may be used for various purposes. A typical use is the production of antibodies specific for binding. These antibodies may be either polyclonal or monoclonal, and may be produced by in vitro or in vivo techniques well known in the art. For production of polyclonal antibodies, an appropriate target immune system, typically mouse or rabbit, is selected. Substantially purified antigen is presented to the immune system in a fashion determined by methods appropriate for the animal and by other parameters well known to immunologists. Typical sites for injection are in footpads, intramuscularly, intraperitoneally, or intradermally. Of course, other species may be substituted for mouse or rabbit. Polyclonal antibodies are then purified using techniques known in the art, adjusted for the desired specificity.

An immunological response is usually assayed with an immunoassay. Normally, such immunoassays involve some purification of a source of antigen, for example, that produced by the same cells and in the same fashion as the antigen. A variety of immunoassay methods are well known in the art. See, e.g., Harlow & Lane, 1988, or Goding, 1986.

Monoclonal antibodies with affinities of 10^{-8} M^{-1} or preferably 10^{-9} to 10^{-10} M^{-1} or stronger will typically be made by standard procedures as described, e.g., in Harlow & Lane, 1988 or Goding, 1986. Briefly, appropriate animals will be selected and the desired immunization protocol followed. After the appropriate period of time, the spleens of such animals are excised and individual spleen cells fused, typically, to immortalized myeloma cells under appropriate selection conditions. Thereafter, the cells are clonally separated and the supernatants of each clone tested for their production of an appropriate antibody specific for the desired region of the antigen.

Other suitable techniques involve in vitro exposure of lymphocytes to the antigenic polypeptides, or alternatively, to selection of libraries of antibodies in phage or similar vectors. See Huse et al., 1989. The polypeptides and antibodies of the present invention may be used with or without modification. Frequently, polypeptides and antibodies will be labeled by joining, either covalently or non-covalently, a substance which provides for a detectable signal. A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent agents, chemiluminescent agents, magnetic particles and the like. Patents teaching the use of such labels include U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149 and 4,366,241. Also, recombinant immunoglobulins may be produced (see U.S. Pat. No. 4,816,567).

"Binding partner" refers to a molecule capable of binding a ligand molecule with high specificity, as for example, an antigen and an antigen-specific antibody or an enzyme and its inhibitor. In general, the specific binding partners must bind with sufficient affinity to immobilize the analyte copy/complementary strand duplex (in the case of polynucleotide hybridization) under the isolation conditions. Specific binding partners are known in the art and include, for example, biotin and avidin or streptavidin, IgG and protein A, the numerous, known receptor-ligand couples, and complementary polynucleotide strands. In the case of complementary polynucleotide binding partners, the partners are normally at least about 15 bases in length, and may be at least 40 bases in length. The polynucleotides may be composed of DNA, RNA, or synthetic nucleotide analogs.

A "biological sample" refers to a sample of tissue or fluid suspected of containing an analyte polynucleotide or polypeptide from an individual including, but not limited to, e.g., plasma, serum, spinal fluid, lymph fluid, the external sections of the skin, respiratory, intestinal, and genitourinary tracts, tears, saliva, blood cells, tumors, organs, tissue and samples of in vitro cell culture constituents.

As used herein, the terms "diagnosing" or "prognosing," as used in the context of neoplasia, are used to indicate 1) the classification of lesions as neoplasia, 2) the determination of the severity of the neoplasia, or 3) the monitoring of the disease progression, prior to, during and after treatment.

"Encode" A polynucleotide is said to "encode" a polypeptide if, in its native state or when manipulated by methods well known to those skilled in the art, it can be transcribed and/or translated to produce the mRNA for and/or the polypeptide or a fragment thereof. The anti-sense strand is the complement of such a nucleic acid, and the encoding sequence can be deduced therefrom.

"Isolated" or "substantially pure". An "isolated" or "substantially pure" nucleic acid (e.g., an RNA, DNA or a mixed polymer) is one which is substantially separated from other cellular components which naturally accompany a native human sequence or protein, e.g., ribosomes, polymerases, many other human genome sequences and proteins. The term embraces a nucleic acid sequence or protein which has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems.

"BRCA2 Allele" refers to normal alleles of the BRCA2 locus as well as alleles carrying variations that predispose individuals to develop cancer of many sites including, for example, breast, ovarian and stomach cancer. Such predisposing alleles are also called "BRCA2 susceptibility alleles".

"BRCA2 Locus," "BRCA2 Gene," "BRCA2 Nucleic Acids" or "BRCA2 Polynucleotide" each refer to polynucleotides, all of which are in the BRCA2 region, that are likely to be expressed in normal tissue, certain alleles of which predispose an individual to develop breast, ovarian and stomach cancers. Mutations at the BRCA2 locus may be involved in the initiation and/or progression of other types of tumors. The locus is indicated in part by mutations that predispose individuals to develop cancer. These mutations fall within the BRCA2 region described infra. The BRCA2 locus is intended to include coding sequences, intervening sequences and regulatory elements controlling transcription and/or translation. The BRCA2 locus is intended to include all allelic variations of the DNA sequence.

These terms, when applied to a nucleic acid, refer to a nucleic acid which encodes a BRCA2 polypeptide, fragment, homolog or variant, including, e.g., protein fusions or deletions. The nucleic acids of the present invention will possess a sequence which is either derived from, or substantially similar to a natural BRCA2-encoding gene or one having substantial homology with a natural BRCA2-encoding gene or a portion thereof. The coding sequence for a BRCA2 polypeptide is shown in SEQ ID NO:1 and FIG. 3, with the amino acid sequence shown in SEQ ID NO:2.

The polynucleotide compositions of this invention include RNA, cDNA, genomic DNA, synthetic forms, and mixed polymers, both sense and antisense strands, and may be chemically or biochemically modified or may contain non-natural or derivatized nucleotide bases, as will be readily appreciated by those skilled in the art. Such modifications include, for example, labels, methylation, substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoamidates, carbamates, etc.), charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), pendent moieties (e.g., polypeptides), intercalators (e.g., acridine, psoralen, etc.), chelators, alkylators, and modified linkages (e.g., alpha anomeric nucleic acids, etc.). Also included are synthetic molecules that mimic polynucleotides in their ability to bind to a designated sequence via hydrogen bonding and other chemical interactions. Such molecules are known in the art and include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule.

The present invention provides recombinant nucleic acids comprising all or part of the BRCA2 region. The recombinant construct may be capable of replicating autonomously in a host cell. Alternatively, the recombinant construct may become integrated into the chromosomal DNA of the host cell. Such a recombinant polynucleotide comprises a polynucleotide of genomic, cDNA, semi-synthetic, or synthetic origin which, by virtue of its origin or manipulation, 1) is not associated with all or a portion of a polynucleotide with which it is associated in nature; 2) is linked to a polynucleotide other than that to which it is linked in nature; or 3) does not occur in nature.

Therefore, recombinant nucleic acids comprising sequences otherwise not naturally occurring are provided by this invention. Although the wild-type sequence may be employed, it will often be altered, e.g., by deletion, substitution or insertion.

cDNA or genomic libraries of various types may be screened as natural sources of the nucleic acids of the present invention, or such nucleic acids may be provided by amplification of sequences resident in genomic DNA or other natural sources, e.g., by PCR. The choice of cDNA libraries normally corresponds to a tissue source which is abundant in mRNA for the desired proteins. Phage libraries are normally preferred, but other types of libraries may be used. Clones of a library are spread onto plates, transferred to a substrate for screening, denatured and probed for the presence of desired sequences.

The DNA sequences used in this invention will usually comprise at least about five codons (nucleotides), more usually at least about 7–15 codons, and most preferably, at least about 35 codons. One or more introns may also be present. This number of nucleotides is usually about the minimal length required for a successful probe that would hybridize specifically with a BRCA2-encoding sequence.

Techniques for nucleic acid manipulation are described generally, for example, in Sambrook et al., 1989 or Ausubel et al., 1992. Reagents useful in applying such techniques, such as restriction enzymes and the like, are widely known in the art and commercially available from such vendors as New England BioLabs, Boehringer Mannheim, Amersham, Promega Biotec, U. S. Biochemicals, New England Nuclear, and a number of other sources. The recombinant nucleic acid sequences used to produce fusion proteins of the present invention may be derived from natural or synthetic sequences. Many natural gene sequences are obtainable from various cDNA or from genomic libraries using appropriate probes. See, GenBank, National Institutes of Health.

"BRCA2 Region" refers to a portion of human chromosome 13 bounded by the markers tdj3820 and YS-G-B10T. This region contains the BRCA2 locus, including the BRCA2 gene.

As used herein, the terms "BRCA2 locus," "BRCA2 allele" and "BRCA2 region" all refer to the double-stranded DNA comprising the locus, allele, or region, as well as either of the single-stranded DNAs comprising the locus, allele or region.

As used herein, a "portion" of the BRCA2 locus or region or allele is defined as having a minimal size of at least about eight nucleotides, or preferably about 15 nucleotides, or more preferably at least about 25 nucleotides, and may have a minimal size of at least about 40 nucleotides.

"BRCA2 protein" or "BRCA2 polypeptide" refer to a protein or polypeptide encoded by the BRCA2 locus, variants or fragments thereof. The term "polypeptide" refers to a polymer of amino acids and its equivalent and does not refer to a specific length of the product; thus, peptides, oligopeptides and proteins are included within the definition of a polypeptide. This term also does not refer to, or exclude modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations, and the like. Included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), polypeptides with substituted linkages as well as other modifications known in the art, both naturally and non-naturally occurring. Ordinarily, such polypeptides will be at least about 50% homologous to the native BRCA2sequence, preferably in excess of about 90%, and more preferably at least about 95% homologous. Also included are proteins encoded by DNA which hybridize under high or low stringency conditions, to BRCA2-encoding nucleic acids and closely related polypeptides or proteins retrieved by antisera to the BRCA2 protein (s).

The length of polypeptide sequences compared for homology will generally be at least about 16 amino acids, usually at least about 20 residues, more usually at least about 24 residues, typically at least about 28 residues, and preferably more than about 35 residues.

"Operably linked" refers to a juxtaposition wherein the components so described are in a relationship permitting them to function in their intended manner. For instance, a promoter is operably linked to a coding sequence if the promoter affects its transcription or expression.

"Probes". Polynucleotide polymorphisms associated with BRCA2 alleles which predispose to certain cancers or are associated with most cancers are detected by hybridization with a polynucleotide probe which forms a stable hybrid with that of the target sequence, under stringent to moderately stringent hybridization and wash conditions. If it is expected that the probes will be perfectly complementary to the target sequence, stringent conditions will be used. Hybridization stringency may be lessened if some mismatching is expected, for example, if variants are expected with the result that the probe will not be completely complementary. Conditions are chosen which rule out nonspecific/adventitious bindings, that is, which minimize noise. Since such indications identify neutral DNA polymorphisms as well as mutations, these indications need further analysis to demonstrate detection of a BRCA2susceptibility allele.

Probes for BRCA2 alleles may be derived from the sequences of the BRCA2 region or its cDNAs. The probes may be of any suitable length, which span all or a portion of the BRCA2 region, and which allow specific hybridization to the BRCA2 region. If the target sequence contains a sequence identical to that of the probe, the probes may be short, e.g., in the range of about 8–30 base pairs, since the hybrid will be relatively stable under even stringent conditions. If some degree of mismatch is expected with the probe, i.e., if it is suspected that the probe will hybridize to a variant region, a longer probe may be employed which hybridizes to the target sequence with the requisite specificity.

The probes will include an isolated polynucleotide attached to a label or reporter molecule and may be used to isolate other polynucleotide sequences, having sequence similarity by standard methods. For techniques for preparing and labeling probes see, e.g., Sambrook et al., 1989 or Ausubel et al., 1992. Other similar polynucleotides may be selected by using homologous is polynucleotides. Alternatively, polynucleotides encoding these or similar polypeptides may be synthesized or selected by use of the redundancy in the genetic code. Various codon substitutions may be introduced, e.g., by silent changes (thereby producing various restriction sites) or to optimize expression for a particular system. Mutations may be introduced to modify the properties of the polypeptide, perhaps to change ligand-binding affinities, interchain affinities, or the polypeptide degradation or turnover rate.

Probes comprising synthetic oligonucleotides or other polynucleotides of the present invention may be derived from naturally occurring or recombinant single- or double-stranded polynucleotides, or be chemically synthesized. Probes may also be labeled by nick translation, Klenow fill-ill reaction, or other methods known in the art.

Portions of the polynucleotide sequence having at least about eight nucleotides, usually at least about 15 nucleotides, and fewer than about 6 kb, usually fewer than about 1.0 kb, from a polynucleotide sequence encoding BRCA2 are preferred as probes. The probes may also be used to determine whether mRNA encoding BRCA2 is present in a cell or tissue.

"Protein modifications or fragments" are provided by the present invention for BRCA2 polypeptides or fragments thereof which are substantially homologous to primary structural sequence but which include e.g., in vivo or in vitro chemical and biochemical modifications or which incorporate unusual amino acids. Such modifications include, for example, acetylation, carboxylation, phosphorylation, glycosylation, ubiquitination, labeling, e.g., with radionuclides, and various enzymatic modifications, as will be readily appreciated by those well skilled in the art.

A variety of methods for labeling polypeptides and of substituents or labels useful for such purposes are well known in the art, and include radioactive isotopes such as ^{32}P, ligands which bind to labeled antiligands (e.g., antibodies), fluorophores, chemiluminescent agents, enzymes, and antiligands which can serve as specific binding pair members for a labeled ligand. The choice of label depends on the sensitivity required, ease of conjugation with the primer, stability requirements, and available instrumentation. Methods of labeling polypeptides are well known in the art. See, e.g., Sambrook et al., 1989 or Ausubel et al., 1992.

Besides substantially full-length polypeptides, the present invention provides for biologically active fragments of the polypeptides. Significant biological activities include ligand-binding, immunological activity and other biological activities characteristic of BRCA2 polypeptides. Immunological activities include both immunogenic function in a target immune system, as well as sharing of immunological epitopes for binding, serving as either a competitor or substitute antigen for an epitope of the BRCA2 protein. As used herein, "epitope" refers to an antigenic determinant of a polypeptide. An epitope could comprise three amino acids in a spatial conformation which is unique to the epitope. Generally, an epitope consists of at least five such amino acids, and more usually consists of at least 8–10 such amino acids. Methods of determining the spatial conformation of such amino acids are known in the art.

For immunological purposes, tandem-repeat polypeptide segments may be used as immunogens, thereby producing highly antigenic proteins. Alternatively, such polypeptides will serve as highly efficient competitors for specific binding. Production of antibodies specific for BRCA2 polypeptides or fragments thereof is described below.

The present invention also provides for fusion polypeptides, comprising BRCA2 polypeptides and fragments. Homologous polypeptides may be fusions between two or more BRCA2 polypeptide sequences or between the sequences of BRCA2 and a related protein. Likewise, heterologous fusions may be constructed which would exhibit a combination of properties or activities of the derivative proteins. For example, ligand-binding or other domains may be "swapped" between different new fusion polypeptides or fragments. Such homologous or heterologous fusion polypeptides may display, for example, altered strength or specificity of binding. Fusion partners include immunoglobulins, bacterial β-galactosidase, trpE, protein A, β-lactamase, alpha amylase, alcohol dehydrogenase and yeast alpha mating factor. See, e.g., Godowski et al., 1988.

Fusion proteins will typically be made by either recombinant nucleic acid methods, as described below, or may be chemically synthesized. Techniques for the synthesis of polypeptides are described, for example, in Merrifield, 1963.

"Protein purification" refers to various methods for the isolation of the BRCA2 polypeptides from other biological material, such as from cells transformed with recombinant nucleic acids encoding BRCA2, and are well known in the art. For example, such polypeptides may be purified by immunoaffinity chromatography employing, e.g., the antibodies provided by the present invention. Various methods of protein purification are well known in the art, and include those described in Deutscher, 1990 and Scopes, 1982.

The terms "isolated", "substantially pure", and "substantially homogeneous" are used interchangeably to describe a protein or polypeptide which has been separated from components which accompany it in its natural state. A monomeric protein is substantially pure when at least about 60 to 75% of a sample exhibits a single polypeptide sequence. A substantially pure protein will typically comprise about 60 to 90% w/w of a protein sample, more usually about 95%, and preferably will be over about 99% pure. Protein purity or homogeneity may be indicated by a number of means well known in the art, such as polyacrylamide gel electrophoresis of a protein sample, followed by visualizing a single polypeptide band upon staining the gel. For certain purposes, higher resolution may be provided by using HPLC or other means well known in the art which are utilized for purification.

A BRCA2 protein is substantially free of naturally associated components when it is separated from the native contaminants which accompany it in its natural state. Thus, a polypeptide which is chemically synthesized or synthesized in a cellular system different from the cell from which it naturally originates will be substantially free from its naturally associated components. A protein may also be rendered substantially free of naturally associated components by isolation, using protein purification techniques well known in the art.

A polypeptide produced as an expression product of an isolated and manipulated genetic sequence is an "isolated polypeptide," as used herein, even if expressed in a homologous cell type. Synthetically made forms or molecules expressed by heterologous cells are inherently isolated molecules.

"Recombinant nucleic acid" is a nucleic acid which is not naturally occurring, or which is made by the artificial combination of two otherwise separated segments of sequence. This artificial combination is often accomplished by either chemical synthesis means, or by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques. Such is usually done to replace a codon with a redundant codon encoding the same or a conservative amino acid, while typically introducing or removing a sequence recognition site. Alternatively, it is performed to join together nucleic acid segments of desired functions to generate a desired combination of fmnctions.

"Regulatory sequences" refers to those sequences normally within 100 kb of the coding region of a locus, but they may also be more distant from the coding region, which affect the expression of the gene (including transcription of the gene, and translation, splicing, stability or the like of the messenger RNA).

"Substantial homology or similarity". A nucleic acid or fragment thereof is "substantially homologous" ("or substantially similar") to another if, when optimally aligned (with appropriate nucleotide insertions or deletions) with the other nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 60% of the nucleotide bases, usually at least about 70%, more usually at least about 80%, preferably at least about 90%, and more preferably at least about 95–98% of the nucleotide bases.

Alternatively, substantial homology or (similarity) exists when a nucleic acid or fragment thereof will hybridize to another nucleic acid (or a complementary strand thereof) under selective hybridization conditions, to a strand, or to its complement. Selectivity of hybridization exists when hybridization which is substantially more selective than total lack of specificity occurs. Typically, selective hybridization will occur when there is at least about 55% homology over a stretch of at least about 14 nucleotides, preferably at least about 65%, more preferably at least about 75%, and most preferably at least about 90%. See, Kanehisa, 1984. The length of homology comparison, as described, may be over longer stretches, and in certain embodiments will often be over a stretch of at least about nine nucleotides, usually at least about 20 nucleotides, more usually at least about 24 nucleotides, typically at least about 28 nucleotides, more typically at least about 32 nucleotides, and preferably at least about 36 or more nucleotides.

Nucleic acid hybridization will be affected by such conditions as salt concentration, temperature, or organic solvents, in addition to the base composition, length of the complementary strands, and the number of nucleotide base mismatches between the hybridizing nucleic acids, as will be readily appreciated by those skilled in the art. Stringent temperature conditions will generally include temperatures in excess of 30° C., typically in excess of 37° C., and preferably in excess of 45° C. Stringent salt conditions will ordinarily be less than 1000 mM, typically less than 500 mM, and preferably less than 200 mM. However, the combination of parameters is much more important than the measure of any single paramneter. See, e.g., Wetmur & Davidson, 1968.

Probe sequences may also hybridize specifically to duplex DNA under certain conditions to form triplex or other higher order DNA complexes. The preparation of such probes and suitable hybridization conditions are well known in the art.

The terms "substantial homology" or "substantial identity", when referring to polypeptides, indicate that the polypeptide or protein in question exhibits at least about 30% identity with an entire naturally-occurring protein or a portion thereof, usually at least about 70% identity, and preferably at least about 95% identity.

"Substantially similar function" refers to the function of a modified nucleic acid or a modified protein, with reference to the wild-type BRCA2 nucleic acid or wild-type BRCA2 polypeptide. The modified polypeptide will be substantially homologous to the wild-type BRCA2 polypeptide and will have substantially the same function. The modified polypeptide may have an altered amino acid sequence and/or may contain modified amino acids. In addition to the similarity of function, the modified polypeptide may have other useful properties, such as a longer half-life. The similarity of function (activity) of the modified polypeptide may be substantially the same as the activity of the wild-type BRCA2 polypeptide. Alternatively, the similarity of function (activity) of the modified polypeptide may be higher than the activity of the wild-type BRCA2 polypeptide. The modified polypeptide is synthesized using conventional techniques, or is encoded by a modified nucleic acid and produced using conventional techniques. The modified nucleic acid is prepared by conventional techniques. A nucleic acid with a function substantially similar to the wild-type BRCA2 gene function produces the modified protein described above.

Homology, for polypeptides, is typically measured using sequence analysis software. See, e.g., the Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 910 University Avenue, Madison, Wis. 53705. Protein analysis software matches similar sequences using measure of homology assigned to various substitutions, deletions and other modifications. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine.

A polypeptide "fragment," "portion" or "segment" is a stretch of amino acid residues of at least about five to seven contiguous amino acids, often at least about seven to nine contiguous amino acids, typically at least about nine to 13 contiguous amino acids and, most preferably, at least about 20 to 30 or more contiguous amino acids.

The polypeptides of the present invention, if soluble, may be coupled to a solid-phase support, e.g., nitrocellulose, nylon, column packing materials (e.g., Sepharose beads), magnetic beads, glass wool, plastic, metal, polymer gels, cells, or other substrates. Such supports may take the form, for example, of beads, wells, dipsticks, or membranes.

"Target region" refers to a region of the nucleic acid which is amplified and/or detected. The term "target sequence" refers to a sequence with which a probe or primer will form a stable hybrid under desired conditions.

The practice of the present invention employs, unless otherwise indicated, conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA, genetics, and immunology. See, e.g., Maniatis et al., 1982; Sambrook et al., 1989; Ausubel et al., 1992; Glover, 1985; Anand, 1992; Guthrie & Fink, 1991. A general discussion of techniques and materials for human gene mapping, including mapping of human chromosome 13, is provided, e.g., in White and Lalouel, 1988.

Preparation of recombinant or chemically synthesized nucleic acids; vectors, transformation, host cells

Large amounts of the polynucleotides of the present invention may be produced by replication in a suitable host cell. Natural or synthetic polynucleotide fragments coding for a desired fragment will be incorporated into recombinant polynucleotide constructs, usually DNA constructs, capable of introduction into and replication in a prokaryotic or eukaryotic cell. Usually the polynucleotide constructs will be suitable for replication in a unicellular host, such as yeast or bacteria, but may also be intended for introduction to (with and without integration within the genome) cultured mammalian or plant or other eukaryotic cell lines. The purification of nucleic acids produced by the methods of the present invention is described, e.g., in Sambrook et al., 1989 or Ausubel et al., 1992.

The polynucleotides of the present invention may also be produced by chemical synthesis, e.g., by the phosphoramidite method described by Beaucage & Carruthers, 1981 or the triester method according to Matteucci and Caruthers, 1981, and may be performed on commercial, automated oligonucleotide synthesizers. A double-stranded fragment may be obtained from the single-stranded product of chemical synthesis either by synthesizing the complementary strand and annealing the strands together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Polynucleotide constructs prepared for introduction into a prokaryotic or eukaryotic host may comprise a replication system recognized by the host, including the intended polynucleotide fragment encoding the desired polypeptide, and will preferably also include transcription and translational initiation regulatory sequences operably linked to the polypeptide encoding segment. Expression vectors may include, for example, an origin of replication or autonomously replicating sequence (ARS) and expression control sequences, a promoter, an enhancer and necessary processing information sites, such as ribosome-binding sites, RNA splice sites, polyadenylation sites, transcriptional terminator sequences, and mRNA stabilizing sequences. Secretion signals may also be included where appropriate, whether from a native BRCA2 protein or from other receptors or from secreted polypeptides of the same or related species, which allow the protein to cross and/or lodge in cell membranes, and thus attain its functional topology, or be secreted from the cell. Such vectors may be prepared by means of standard recombinant techniques well known in the art and discussed, for example, in Sambrook et al., 1989 or Ausubel et al. 1992.

An appropriate promoter and other necessary vector sequences will be selected so as to be functional in the host, and may include, when appropriate, those naturally associated with BRCA2 genes. Examples of workable combinations of cell lines and expression vectors are described in Sambrook et al., 1989 or Ausubel et al., 1992; see also, e.g., Metzger et al., 1988. Many useful vectors are known in the art and may be obtained from such vendors as Stratagene, New England BioLabs, Promega Biotech, and others. Promoters such as the trp, lac and phage promoters, tRNA promoters and glycolytic enzyme promoters may be used in prokaryotic hosts. Useful yeast promoters include promoter regions for metallothionein, 3-phosphoglycerate kinase or other glycolytic enzymes such as enolase or glyceraldehyde-3-phosphate dehydrogenase, enzymes responsible for maltose and galactose utilization, and others. Vectors and promoters suitable for use in yeast expression are further described in Hitzeman et al., EP 73,675A. Appropriate non-native mammalian promoters might include the early and late promoters from SV40 (Fiers et al., 1978) or promoters derived from murine Moloney leukemia virus, mouse tumor virus, avian sarcoma viruses, adenovirus II, bovine papilloma virus or polyoma. In addition, the construct may be joined to an amplifiable gene (e.g., DHFR) so that multiple copies of the gene may be made. For appropriate enhancer and other expression control sequences, see also *Enhancers and Eukaryotic Gene Expression*, Cold Spring Harbor Press, Cold Spring Harbor, N.Y. (1983).

While such expression vectors may replicate autonomously, they may also replicate by being inserted into the genome of the host cell, by methods well known in the art.

Expression and cloning vectors will likely contain a selectable marker, a gene encoding a protein necessary for survival or growth of a host cell transformed with the vector. The presence of this gene ensures growth of only those host cells which express the inserts. Typical selection genes encode proteins that a) confer resistance to antibiotics or other toxic substances, e.g. ampicillin, neomycin, methotrexate, etc.; b) complement auxotrophic deficiencies, or c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for Bacilli. The choice of the proper selectable marker will depend on the host cell, and appropriate markers for different hosts are well known in the art.

The vectors containing the nucleic acids of interest can be transcribed in vitro, and the resulting RNA introduced into the host cell by well-known methods, e.g., by injection (see, Kubo et al., 1988), or the vectors can be introduced directly into host cells by methods well known in the art, which vary depending on the type of cellular host, including electroporation; transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; infection (where the vector is an infectious agent, such as a retroviral genome); and other methods. See generally, Sambrook et al., 1989 and Ausubel et al., 1992. The introduction of the polynucleotides into the host cell by any method known in the art, including, inter alia, those described above, will be referred to herein as "transformation." The cells into which have been introduced nucleic acids described above are meant to also include the progeny of such cells.

Large quantities of the nucleic acids and polypeptides of the present invention may be prepared by expressing the BRCA2 nucleic acids or portions thereof in vectors or other expression vehicles in compatible prokaryotic or eukaryotic host cells. The most commonly used prokaryotic hosts are strains of *Escherichia coli*, although other prokaryotes, such as *Bacillus subtilis or Pseudomonas* may also be used.

Mammalian or other eukaryotic host cells, such as those of yeast, filamentous fungi, plant, insect, or amphibian or avian species, may also be useful for production of the proteins of the present invention. Propagation of mammalian cells in culture is per se well known. See, Jakoby and Pastan, 1979. Examples of commonly used mammalian host cell lines are VERO and HeLa cells, Chinese hamster ovary (CHO) cells, and WI38, BHK, and COS cell lines, although it will be appreciated by the skilled practitioner that other cell lines may be appropriate, e.g., to provide higher expression desirable glycosylation patterns, or other features.

Clones are selected by using markers depending on the mode of the vector construction. The marker may be on the same or a different DNA molecule, preferably the same DNA molecule. In prokaryotic hosts, the transformant may be selected, e.g., by resistance to ampicillin, tetracycline or other antibiotics. Production of a particular product based on temperature sensitivity may also serve as an appropriate marker.

Prokaryotic or eukaryotic cells transformed with the polynucleotides of the present invention will be useful not only for the production of the nucleic acids and polypeptides of the present invention, but also, for example, in studying the characteristics of BRCA2 polypeptides.

Antisense polynucleotide sequences are useful in preventing or diminishing the expression of the BRCA2 locus, as will be appreciated by those skilled in the art. For example, polynucleotide vectors containing all or a portion of the BRCA2 locus or other sequences from the BRCA2 region (particularly those flanking the BRCA2 locus) may be placed under the control of a promoter in an antisense orientation and introduced into a cell. Expression of such an antisense construct within a cell will interfere with BRCA2 transcription and/or translation and/or replication.

The probes and primers based on the BRCA2 gene sequences disclosed herein are used to identify homologous BRCA2 gene sequences and proteins in other species. These BRCA2 gene sequences and proteins are used in the diagnostic/prognostic, therapeutic and drug screening methods described herein for the species from which they have been isolated.

Methods of Use: Nucleic Acid Diagnosis and Diagnostic Kits

In order to detect the presence of a BRCA2 allele predisposing an individual to cancer, a biological sample such as blood is prepared and analyzed for the presence or absence of susceptibility alleles of BRCA2. In order to detect the presence of neoplasia, the progression toward malignancy of a precursor lesion, or as a prognostic indicator, a biological sample of the lesion is prepared and analyzed for the presence or absence of mutant alleles of BRCA2. Results of these tests and interpretive information are returned to the health care provider for communication to the tested individual. Such diagnoses may be performed by diagnostic laboratories, or, alternatively, diagnostic kits are manufactured and sold to health care providers or to private individuals for self-diagnosis.

Initially, the screening method involves amplification of the relevant BRCA2sequences. In another preferred embodiment of the invention, the screening method involves a non-PCR based strategy. Such screening methods include two-step label amplification methodologies that are well known in the art. Both PCR and non-PCR based screening strategies can detect target sequences with a high level of sensitivity.

The most popular method used today is target amplification. Here, the target nucleic acid sequence is amplified with polymerases. One particularly preferred method using polymerase- driven amplification is the polymerase chain reaction (PCR). The polymerase chain reaction and other polymerase-driven amplification assays can achieve over a million-fold increase in copy number through the use of polymerase-driven amplification cycles. Once amplified, the resulting nucleic acid can be sequenced or used as a substrate for DNA probes.

When the probes are used to detect the presence of the target sequences (for example, in screening for cancer susceptibility), the biological sample to be analyzed, such as blood or serum, may be treated, if desired, to extract the nucleic acids. The sample nucleic acid may be prepared in various ways to facilitate detection of the target sequence; e.g. denaturation, restriction digestion, electrophoresis or dot blotting. The targeted region of the analyte nucleic acid usually must be at least partially single-stranded to form hybrids with the targeting sequence of the probe. If the sequence is naturally single-stranded, denaturation will not be required. However, if the sequence is double-stranded, the sequence will probably need to be denatured. Denaturation can be carried out by various techniques known in the art.

Analyte nucleic acid and probe are incubated under conditions which promote stable hybrid formation of the target sequence in the probe with the putative targeted sequence in the analyte. The region of the probes which is used to bind to the analyte can be made completely complementary to the targeted region of human chromosome 13. Therefore, high stringency conditions are desirable in order to prevent false positives. However, conditions of high stringency are used only if the probes are complementary to regions of the chromosome which are unique in the genome. The stringency of hybridization is determined by a number of factors during hybridization and during the washing procedure, including temperature, ionic strength, base composition, probe length, and concentration of formamide. These factors are outlined in, for example, Maniatis et al., 1982 and Sambrook et al., 1989. Under certain circumstances, the formation of higher order hybrids, such as triplexes, quadraplexes, etc., may be desired to provide the means of detecting target sequences.

Detection, if any, of the resulting hybrid is usually accomplished by the use of labeled probes. Alternatively, the probe may be unlabeled, but may be detectable by specific binding with a ligand which is labeled, either directly or indirectly. Suitable labels, and methods for labeling probes and ligands are known in the art, and include, for example, radioactive labels which may be incorporated by known methods (e.g., nick translation, random priming or kinasing), biotin, fluorescent groups, chemiluminescent groups (e.g., dioxetanes, particularly triggered dioxetanes), enzymes, antibodies and the like. Variations of this basic scheme are known in the art, and include those variations that facilitate separation of the hybrids to be detected from extraneous materials and/or that amplify the signal from the labeled moiety. A number of these variations are reviewed in, e.g., Matthews & Kricka, 1988; Landegren et al., 1988; Mittlin, 1989; U.S. Pat. No. 4,868,105, and in EPO Publication No. 225,807.

As noted above, non-PCR based screening assays are also contemplated in this invention. An exemplary non-PCR based procedure is provided in Example 6. This procedure hybridizes a nucleic acid probe (or an analog such as a methyl phosphonate backbone replacing the normal phosphodiester), to the low level DNA target. This probe may have an enzyme covalently linked to the probe, such that the covalent linkage does not interfere with the specificity of the hybridization. This enzyme-probe-conjugate-target nucleic acid complex can then be isolated away from the free probe enzyme conjugate and a substrate is added for enzyme detection. Enzymatic activity is observed as a change in color development or luminescent output resulting in a 10^3–10^6 increase in sensitivity. For an example relating to preparation of oligodeoxynucleotide-alkaline phosphatase conjugates and their use as hybridization probes, see Jablonski et al., 1986.

Two-step label amplification methodologies are known in the art. These assays work on the principle that a small ligand (such as digoxigenin, biotin, or the like) is attached to a nucleic acid probe capable of specifically binding BRCA2. Exemplary probes can be developed on the basis of the sequence set forth in SEQ ID NO:1 and FIG. 3 of this patent application. Allele-specific probes are also contemplated within the scope of this example, and exemplary allele specific probes include probes encompassing the predisposing mutations described below, including those described in Table 2.

In one example, the small ligand attached to the nucleic acid probe is specifically recognized by an antibody-enzyme conjugate. In one embodiment of this example, digoxigenin is attached to the nucleic acid probe. Hybridization is detected by an antibody-alkaline phosphatase conjugate which turns over a chemiluminescent substrate. For methods for labeling nucleic acid probes according to this embodiment see Martin et al., 1990. In a second example, the small ligand is recognized by a second ligand-enzyme conjugate that is capable of specifically complexing to the first ligand. A well known embodiment of this example is the biotin-avidin type of interactions. For methods for labeling nucleic acid probes and their use in biotin-avidin based assays see Rigby et al., 1977 and Nguyen et al., 1992.

It is also contemplated within the scope of this invention that the nucleic acid probe assays of this invention will employ a cocktail of nucleic acid probes capable of detecting BRCA2. Thus, in one example to detect the presence of BRCA2 in a cell sample, more than one probe complementary to BRCA2 is employed and in particular the number of different probes is alternatively 2, 3, or 5 different nucleic acid probe sequences. In another example, to detect the presence of mutations in the BRCA2 gene sequence in a patient, more than one probe complementary to BRCA2 is employed where the cocktail includes probes capable of binding to the allele-specific mutations identified in populations of patients with alterations in BRCA2. In this embodiment, any number of probes can be used, and will preferably include probes corresponding to the major gene mutations identified as predisposing an individual to breast cancer. Some candidate probes contemplated within the scope of the invention include probes that include the allele-specific mutations described below and those that have the BRCA2 regions shown in SEQ ID NO:1 and FIG. 3, both 5' and 3' to the mutation site.

Methods of Use: Peptide Diagnosis and Diagnostic Kits

The neoplastic condition of lesions can also be detected on the basis of the alteration of wild-type BRCA2 polypeptide. Such alterations can be determined by sequence analysis in accordance with conventional techniques. More preferably, antibodies (polyclonal or monoclonal) are used to detect differences in, or the absence of BRCA2 peptides. The antibodies may be prepared as discussed above under the heading "Antibodies" and as further shown in Examples 9 and 10. Other techniques for raising and purifying antibodies are well known in the art and any such techniques may be chosen to achieve the preparations claimed in this invention. In a preferred embodiment of the invention, antibodies will immunoprecipitate BRCA2 proteins from solution as well as react with BRCA2 protein on Western or immunoblots of polyacrylamide gels. In another preferred embodiment, antibodies will detect BRCA2 proteins in paraffin or frozen tissue sections, using immunocytochemical techniques.

Preferred embodiments relating to methods for detecting BRCA2 or its mutations include enzyme linked immunosorbent assays (ELISA), radioimmunoassays (RIA), immunoradiometric assays (IRMA) and immunoenzymatic assays (IEMA), including sandwich assays using monoclonal and/or polyclonal antibodies. Exemplary sandwich assays are described by David et al. in U.S. Pat. Nos. 4,376,110 and 4,486,530, hereby incorporated by reference, and exemplified in Example 9.

Methods of Use: Drug Screening

This invention is particularly useful for screening compounds by using the BRCA2 polypeptide or binding fragment thereof in any of a variety of drug screening techniques.

The BRCA2 polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, or borne on a cell surface. One method of drug screening utilizes eucaryotic or procaryotic host cells which are stably transformed with recombinant polynucleotides expressing the polypeptide or fragment, preferably in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, for the formation of complexes between a BRCA2 polypeptide or fragment and the agent being tested, or examine the degree to which the formation of a complex between a BRCA2 polypeptide or fragment and a known ligand is interfered with by the agent being tested.

Thus, the present invention provides methods of screening for drugs comprising contacting such an agent with a BRCA2 polypeptide or fragment thereof and assaying (i) for the presence of a complex between the agent and the BRCA2 polypeptide or fragment, or (ii) for the presence of a complex between the BRCA2 polypeptide or fragment and a ligand, by methods well known in the art. In such competitive binding assays the BRCA2 polypeptide or fragment is typically labeled. Free BRCA2 polypeptide or fragment is separated from that present in a protein:protein complex, and the amount of free (i.e., uncomplexed) label is a measure of the binding of the agent being tested to BRCA2 or its interference with BRCA2: ligand binding, respectively.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the BRCA2 polypeptides and is described in detail in Geysen, PCT published application WO 84/03564, published on Sep. 13, 1984. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with BRCA2 polypeptide and washed. Bound BRCA2 polypeptide is then detected by methods well known in the art. Purified BRCA2 can be coated directly onto plates for use in the aforementioned drug screening techniques. However, non-neutralizing antibodies to the polypeptide can be used to capture antibodies to immobilize the BRCA2 polypeptide on the solid phase.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of specifically binding the BRCA2 polypeptide compete with a test compound for binding to the BRCA2 polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants of the BRCA2 polypeptide.

A further technique for drug screening involves the use of host eukaryotic cell lines or cells (such as described above) which have a nonfunctional BRCA2 gene. These host cell lines or cells are defective at the BRCA2 polypeptide level. The host cell lines or cells are grown in the presence of drug compound. The rate of growth of the host cells is measured to determine if the compound is capable of regulating the growth of BRCA2 defective cells.

Methods of Use: Rational Drug Design

The goal of rational drug design is to produce structural analogs of biologically active polypeptides of interest or of small molecules with which they interact (e.g., agonists, antagonists, inhibitors) in order to fashion drugs which are, for example, more active or stable forms of the polypeptide, or which, e.g., enhance or interfere with the function of a polypeptide in vivo. See, e.g., Hodgson, 1991. In one approach, one first determines the three-dimensional structure of a protein of interest (e.g., BRCA2 polypeptide) or, for example, of the BRCA2-receptor or ligand complex, by x-ray crystallography, by computer modeling or most typically, by a combination of approaches. Less often, useful information regarding the structure of a polypeptide may be gained by modeling based on the structure of homologous proteins. An example of rational drug design is the development of HIV protease inhibitors (Erickson et al., 1990). In addition, peptides (e.g., BRCA2 polypeptide) are analyzed by an alanine scan (Wells, 1991). In this technique, an amino acid residue is replaced by Ala, and its effect on the peptide's activity is determined. Each of the amino acid residues of the peptide is analyzed in this manner to determine the important regions of the peptide.

It is also possible to isolate a target-specific antibody, selected by a functional assay, and then to solve its crystal structure. In principle, this approach yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced banks of peptides. Selected peptides would then act as the pharmacore.

Thus, one may design drugs which have, e.g., improved BRCA2 polypeptide activity or stability or which act as inhibitors, agonists, antagonists, etc. of BRCA2 polypeptide activity. By virtue of the availability of cloned BRCA2sequences, sufficient amounts of the BRCA2 polypeptide may be made available to perform such analytical studies as x-ray crystallography. In addition, the knowledge of the BRCA2 protein sequence provided herein will guide those employing computer modeling techniques in place of, or in addition to x-ray crystallography.

Methods of Use: Gene Therapy

According to the present invention, a method is also provided of supplying wild-type BRCA2 function to a cell which carries mutant BRCA2 alleles. Supplying such a function should suppress neoplastic growth of the recipient cells. The wild-type BRCA2 gene or a part of the gene may be introduced into the cell in a vector such that the gene remains extrachromosomal. In such a situation, the gene will be expressed by the cell from the extrachromosomal location. If a gene fragment is introduced and expressed in a cell carrying a mutant BRCA2 allele, the gene fragment should encode a part of the BRCA2 protein which is required for non-neoplastic growth of the cell. More preferred is the situation where the wild-type BRCA2 gene or a part thereof is introduced into the mutant cell in such a way that it recombines with the endogenous mutant BRCA2 gene present in the cell. Such recombination requires a double recombination event which results in the correction of the BRCA2 gene mutation. Vectors for introduction of genes both for recombination and for extrachromosomal maintenance are known in the art, and any suitable vector may be used. Methods for introducing DNA into cells such as electroporation, calcium phosphate co-precipitation and viral transduction are known in the art, and the choice of method is within the competence of the routineer. Cells transformed with the wild-type BRCA2 gene can be used as model systems to study cancer remission and drug treatments which promote such remission.

As generally discussed above, the BRCA2 gene or fragment, where applicable, may be employed in gene therapy methods in order to increase the amount of the expression products of such genes in cancer cells. Such gene therapy is particularly appropriate for use in both cancerous and pre-cancerous cells, in which the level of BRCA2 polypeptide is absent or diminished compared to normal cells. It may also be useful to increase the level of expression of a given BRCA2 gene even in those tumor cells in which the mutant gene is expressed at a "normal" level, but the gene product is not fully functional.

Gene therapy would be carried out according to generally accepted methods, for example, as described by Friedman, 1991. Cells from a patient's tumor would be first analyzed by the diagnostic methods described above, to ascertain the production of BRCA2 polypeptide in the tumor cells. A virus or plasmid vector (see further details below), containing a copy of the BRCA2 gene linked to expression control elements and capable of replicating inside the tumor cells, is prepared. Suitable vectors are known, such as disclosed in U.S. Pat. No. 5,252,479 and PCT published application WO 93/07282. The vector is then injected into the patient, either locally at the site of the tumor or systemically (in order to reach any tumor cells that may have metastasized to other sites). If the transfected gene is not permanently incorporated into the genome of each of the targeted tumor cells, the treatment may have to be repeated periodically.

Gene transfer systems known in the art may be useful in the practice of the gene therapy methods of the present invention. These include viral and nonviral transfer methods. A number of viruses have been used as gene transfer vectors, including papovaviruses, e.g., SV40 (Madzak et al., 1992), adenovirus (Berkner, 1992; Berkner et al., 1988; Gorziglia and Kapikian, 1992; Quantin et al., 1992; Rosenfeld et al., 1992; Wilkinson et al., 1992; Stratford-Perricaudet et al., 1990), vaccinia virus (Moss, 1992), adeno-associated virus (Muzyczka, 1992; Ohi et al., 1990), herpesviruses including HSV and EBV (Margolskee, 1992; Johnson et al., 1992; Fink et al., 1992; Breakfield and Geller, 1987; Freese et al., 1990), and retroviruses of avian (Brandyopadhyay and Temin, 1984; Petropoulos et al., 1992), murine (Miller, 1992; Miller et al., 1985; Sorge et al., 1984; Mann and Baltimore, 1985; Miller et al., 1988), and human origin (Shimada et al., 1991; Helseth et al., 1990; Page et al., 1990; Buchschacher and Panganiban, 1992). Most human gene therapy protocols have been based on disabled murine retroviruses.

Nonviral gene transfer methods known in the art include chemical techniques such as calcium phosphate coprecipitation (Graham and van der Eb, 1973; Pellicer et al., 1980); mechanical techniques, for example microinjection (Anderson et al., 1980; Gordon et al., 1980; Brinster et al., 1981; Constantini and lacy, 1981); membrane fusion-mediated transfer via liposomes (Felgner et al., 1987; Wang and Huang, 1989; Kaneda et al., 1989; Stewart et al., 1992; Nabel et al., 1990; Lim et al., 1992); and direct DNA uptake and receptor-mediated DNA transfer (Wolff et al., 1990; Wu et al., 1991; Zenke et al., 1990; Wu et al., 1989b; Wolff et al., 1991; Wagner et al., 1990; Wagner et al., 1991; Cotten et al., 1990; Curiel et al., 1991a; Curiel et al., 1991b). Viral-mediated gene transfer can be combined with direct in vivo gene transfer using liposome delivery, allowing one to direct the viral vectors to the tumor cells and not into the surrounding nondividing cells. Alternatively, the retroviral vector producer cell line can be injected into tumors (Culver et al., 1992). Injection of producer cells would then provide a continuous source of vector particles. This technique has been approved for use in humans with inoperable brain tumors.

In an approach which combines biological and physical gene transfer methods, plasmid DNA of any size is combined with a polylysine-conjugated antibody specific to the adenovirus hexon protein, and the resulting complex is bound to an adenovirus vector. The trimolecular complex is then used to infect cells. The adenovirus vector permits efficient binding, internalization, and degradation of the endosome before the coupled DNA is damaged.

Liposome/DNA complexes have been shown to be capable of mediating direct in vivo gene transfer. While in standard liposome preparations the gene transfer process is nonspecific, localized in vivo uptake and expression have been reported in tumor deposits, for example, following direct in situ administration (Nabel, 1992).

Gene transfer techniques which target DNA directly to breast and ovarian tissues, e.g., epithelial cells of the breast or ovaries, is preferred. Receptor-mediated gene transfer, for example, is accomplished by the conjugation of DNA (usually in the form of covalently closed supercoiled plasmid) to a protein ligand via polylysine. Ligands are chosen on the basis of the presence of the corresponding ligand receptors on the cell surface of the target cell/tissue type. One appropriate receptor/ligand pair may include the estrogen receptor and its ligand, estrogen (and estrogen analogues). These ligand-DNA conjugates can be injected directly into the blood if desired and are directed to the target tissue where receptor binding and internalization of the

DNA-protein complex occurs. To overcome the problem of intracellular destruction of DNA, coinfection with adenovirus can be included to disrupt endosome function.

The therapy involves two steps which can be performed singly or jointly. In the first step, prepubescent females who carTy a BRCA2susceptibility allele are treated with a gene delivery vehicle such that some or all of their mammary ductal epithelial precursor cells receive at least one additional copy of a functional normal BRCA2 allele. In this step, the treated individuals have reduced risk of breast cancer to the extent that the effect of the susceptible allele has been countered by the presence of the normal allele. In the second step of a preventive therapy, predisposed young females, in particular women who have received the proposed gene therapeutic treatment, undergo hormonal therapy to mimic the effects on the breast of a full term pregnancy.

Methods of Use: Peptide Therapy

Peptides which have BRCA2 activity can be supplied to cells which carry mutant or missing BRCA2 alleles. The sequence of the BRCA2 protein is disclosed in SEQ ID NO:2. Protein can be produced by expression of the cDNA sequence in bacteria, for example, using known expression vectors. Alternatively, BRCA2 polypeptide can be extracted from BRCA2-producing mammalian cells. In addition, the techniques of synthetic chemistry can be employed to synthesize BRCA2 protein. Any of such techniques can provide the preparation of the present invention which comprises the BRCA2 protein. The preparation is substantially free of other human proteins. This is most readily accomplished by synthesis in a microorganism or in vitro.

Active BRCA2 molecules can be introduced into cells by microinjection or by use of liposomes, for example. Alternatively, some active molecules may be taken up by cells, actively or by diffusion. Extracellular application of the BRCA2 gene product may be sufficient to affect tumor growth. Supply of molecules with BRCA2 activity should lead to partial reversal of the neoplastic state. Other molecules with BRCA2 activity (for example, peptides, drugs or organic compounds) may also be used to effect such a reversal. Modified polypeptides having substantially similar function are also used for peptide therapy.

Methods of Uise: Transformed Hosts

Similarly, cells and animals which carry a mutant BRCA2 allele can be used as model systems to study and test for substances which have potential as therapeutic agents. The cells are typically cultured epithelial cells. These may be isolated from individuals with BRCA2 mutations, either somatic or germline. Alternatively, the cell line can be engineered to carry the mutation in the BRCA2 allele, as described above. After a test substance is applied to the cells, the neoplastically transformed phenotype of the cell is determined. Any trait of neoplastically transformed cells can be assessed, including anchorage-independent growth, tumorigenicity in nude mice, invasiveness of cells, and growth factor dependence. Assays for each of these traits are known in the art.

Animals for testing therapeutic agents can be selected after mutagenesis of whole animals or after treatment of germline cells or zygotes. Such treatments include insertion of mutant BRCA2 alleles, usually from a second animal species, as well as insertion of disrupted homologous genes. Alternatively, the endogenous BRCA2 gene(s) of the animals may be disrupted by insertion or deletion mutation or other genetic alterations using conventional techniques (Capecchi, 1989; Valancius and Smithies, 1991; Hasty et al., 1991; Shinkai et al., 1992; Mombaerts et al., 1992; Philpott et al., 1992; Snouwaert et al., 1992; Donehower et al., 1992). After test substances have been administered to the animals, the growth of tumors must be assessed. If the test substance prevents or suppresses the growth of tumors, then the test substance is a candidate therapeutic agent for the treatment of the cancers identified herein. These animal models provide an extremely important testing vehicle for potential therapeutic products.

The present invention is described by reference to the following Examples, which are offered by way of illustration and are not intended to limit the invention in any manner. Standard techniques well known in the art or the techniques specifically described below were utilized.

EXAMPLE 1

Ascertain and Study Kindreds Likely to Have a Chromosome 13-Linked Breast Cancer Susceptibility Locus

Extensive cancer prone kindreds were ascertained from a defined population providing a large set of extended kindreds with multiple cases of breast cancer and many relatives available to study. The large number of meioses present in these large kindreds provided the power to detect whether the BRCA2 locus was segregating, and increased the opportunity for informative recombinants to occur within the small region being investigated. This vastly improved the chances of establishing linkage to the BRCA2 region, and greatly facilitated the reduction of the BRCA2 region to a manageable size, which permits identification of the BRCA2 locus itself.

Each kindred was extended through all available connecting relatives, and to all informative first degree relatives of each proband or cancer case. For these kindreds, additional breast cancer cases and individuals with cancer at other sites of interest who also appeared in the kindreds were identified through the tumor registry linked files. All breast cancers reported in the kindred which were not confirmed in the Utah Cancer Registry were researched. Medical records or death certificates were obtained for confirmation of all cancers. Each key connecting individual and all informative individuals were invited to participate by providing a blood sample from which DNA was extracted. We also sampled spouses and relatives of deceased cases so that the genotype of the deceased cases could be inferred from the genotypes of their relatives.

Kindreds which had three or more cancer cases with inferable genotypes were selected for linkage studies to chromosome 13 markers. These included kindreds originally ascertained from the linked databases for a study of proliferative breast disease and breast cancer (Skolnick et al., 1990). The criterion for selection of these kindreds was the presence of two sisters or a mother and her daughter with breast cancer. Additionally, kindreds which have been studied since 1980 as part of our breast cancer linkage studies and kindreds ascertained from the linked databases for the presence of clusters of male and female breast cancer and self-referred kindreds with early onset breast cancer were included. These kindreds were investigated and expanded in our clinic in the manner described above.

For each sample collected in these kindreds, DNA was extracted from blood or paraffin- embedded tissue blocks using standard laboratory protocols. Genotyping in this study was restricted to short tandem repeat (STR) markers since, in general, they have high heterozygosity and PCR methods offer rapid turnaround while using very small amounts of DNA. To aid in this effort, STR markers on chromosome 13 were developed by screening a chromosome specific cosmid library for clones which contained short tandem repeats of 2, 3 or 4, localized to the short arm in the region of the Rb tumor suppressor locus. Oligonucleotide sequences for markers not developed in our laboratory were obtained from published reports, or as part of the Breast Cancer Linkage Consortium, or from other investigators. All genotyping films were scored blindly with a standard lane marker used to maintain consistent coding of alleles. Key samples underwent duplicate typing for all relevant markers.

TABLE 1

Haplotype and Phenotype Data for the 18 Families

	Number of Cancer Cases (1)				Posterior	tdj		STRs Examined							
								D13S		mh	D13S	5370-		D13S	D13S
Kindred	FBR	MBR	OV	LOD	Probability (2)	3820	4247	260	GA9	5a1	171	2C	AC6	310	267
107*	22	3	2	5.06	1.00	8	28	4	10	8	*3	2	6	4	12
8001	0	3	0	n.d.	0.90	8	30	6	10	7	10	5	5	5	4
8004	1	2	0	n.d.	0.90	9	11	4	4	7	8	6	8	4	12
2044*	8	1	4	2.13	1.00	9	12	10	7	5	9	6	5	4	8
2043*	2	1	1	0.86	0.98	6	30	3	12	7	10	5	8	4	12
2018	3	1	0	n.d.	0.90	9	12	7	3	8	3	6	6	5	8
937	3	1	0	n.d.	0.90	8	10	4	—	—	8	10	6	7	7
1018*	9	1	0	2.47	1.00	6	17	8	10	5	8	2	5	4	8
2326	11	1	0	0.42	0.96	9	10	3	10	5	8	5	5	7	12
2263	2	1	0	n.d.	0.90	9	28	8	—	8	4	—	—	7	12
8002	2	1	0	n.d.	0.90	3	29	7	10	5	8	5	5	5	8
8003	2	1	0	n.d.	0.90	4	12	6	10	6	3	4	5	4	8
2367	6	0	1	0.40	0.85	6	28	7	10	12	3	7	5	5	4
2388	3	0	1	0.92	0.95	8	16	7	12	4	10	4	5	5	12
2027*	4	0	0	0.39	0.85	4	11	3	10	7	10	5	6	7	12
4328	4	0	0	0.44	0.87	9	10	8	4	8	3	7	8	5	12
2355	3	0	0	0.36	0.84	9	10	6	4	6	..3	7	5	8	8
2327	11	0	0	1.92	0.99	3	12	2	9	5	10	5	5	3	4
1019	2	2	0												

*Families reported in Wooster et al. (1994)

n.d. = not determined

(1) Excludes cases known to be sporadic (i.e., do not share the BRCA2 haplotype segregating in the family).

FBR = female breast cancer under 60 years.

MBR = male breast cancer

OV = ovarian cancer

(2) Posterior probability assumes that, a priori, 90% of families with male breast and early onset female breast cancers that are unlinked to BRCA1 are due to BRCA2, and 70% of female breast cancer families unlinked to BRCA1 are due to BRCA1.

LOD scores for each kindred were calculated for two recombination fraction values, 0.001 and 0.1. (For calculation of LOD scores, see Ott 1985). Likelihoods were computed under the model derived by Claus et al., 1991, which assumes an estimated gene frequency of 0.003, a lifetime risk in female gene carriers of about 0.80, and population based age-specific risks for breast cancer in non-gene carriers. Allele frequencies for the markers used for the LOD score calculations were calculated from our own laboratory typings of unrelated individuals in the CEPH panel (White and Lalouel, 1988).

Kindred 107 is the largest chromosome 13-linked breast cancer family reported to date by any group. The evidence of linkage to chromosome 13 for this family is overwhelming. In smaller kindreds, sporadic cancers greatly confound the analysis of linkage and the correct identification of key recombinants.

In order to improve the characterization of our recombinants and define closer flanking markers, a dense map of this relatively small region on chromosome 13 was required. Our approach was to analyze existing STR markers provided by other investigators and any newly developed markers from our laboratory in our chromosome linked kindreds. FIG. 1 shows the location of ten markers used in the genetic analysis. Table 1 gives the LOD scores for linkage for each of the 19 kindreds in our study, which reduced the region to approximately 1.5 Mb.

Table 1 also gives the posterior probability of a kindred having a BRCA2 mutation based on LOD scores and prior probabilities. Four of these markers (D13S171, D13S260, D13S310 and D13S267) were previously known. The other six markers were found as part of our search for BRCA2. We were able to reduce the region to 1.5 megabases based on a recombinant in Kindred 107 with marker tdj3820 at the left boundary, and a second recombinant in Kindred 2043 with marker YS-G-B10T at the right boundary (see FIG. 1) which is at approximately the same location as AC6 and D13S310. Furthermore, a homozygous deletion was found in a pancreatic tumor cell line in the BRCA2 region which may have been driven by BRCA2 itself, this deletion is referred to as the Schutte/Kern deletion in FIG. 1 (Schutte et al., 1995). The Schutte/Kern contig in FIG. 1 refers to these authors' physical map which covers the deletion.

EXAMPLE 2

Development of Genetic and Physical Resources in the Region of Interest

To increase the number of highly polymorphic loci in the BRCA2 region, we developed a number of STR markers in our laboratory from P1s, BACs and YACs which physically map to the region. These markers allowed us to further refine the region (see Table 1 and the discussion above).

STSs in the desired region were used to identify YACs which contained them. These YACs were then used to identify subclones in P1s or BACs. These subdlones were then screened for the presence of a short tandem repeats. Clones with a strong signal were selected preferentially, since they were more likely to represent repeats which have a large number of repeats and/or are of near- perfect fidelity to the pattern. Both of these characteristics are known to increase the probability of polymorphism (Weber et al., 1990). These clones were sequenced directly from the vector to locate the repeat. We obtained a unique sequence on one side of the short tandem repeat by using one of a set of possible primers complementary to the end of the repeat. Based on this unique sequence, a primer was made to sequence back across the repeat in the other direction, yielding a unique sequence for design of a second primer flanking it. STRs were then screened for polymorphism on a small group of unrelated individuals and tested against the hybrid panel to confirm their physical localization. New markers which satisfied these criteria were then typed in a set of unrelated individuals from Utah to obtain allele frequencies appropriate for the study of this population. Many of the other markers reported in this study were also tested in unrelated individuals to obtain similarly appropriate allele frequencies.

Using the procedure described above, novel STRs were found from these YACs which were both polymorphic and localized to the BRCA2 region. FIG. 1 shows a schematic map of STSs, P1s, BACs and YACs in the BRCA2 region.

EXAMPLE 3

Identification of Candidate cDNA Clones for the BRCA2 Locus by Genomic Analysis of the Contig Region

1. General Methods

Complete screen of the plausible region. The first method to identify candidate cDNAs, although labor intensive, used known techniques. The method comprised the screening of P1 and BAC clones in the contig to identify putative coding sequences. The clones containing putative coding sequences were then used as probes on filters of cDNA libraries to identify candidate cDNA clones for future analysis. The clones were screened for putative coding sequences by either of two methods.

The P1 clones to be analyzed were digested with a restriction enzyme to release the human DNA from the vector DNA. The DNA was separated on a 14 cm, 0.5% agarose gel run overnight at 20 volts for 16 hours. The human DNA bands were cut out of the gel and electroeluted from the gel wedge at 100 volts for at least two hours in 0.5× Tris Acetate buffer (Maniatis et al., 1982). The eluted Not I digested DNA (~15 kb to 25 kb) was then digested with EcoRI restriction enzyme to give smaller fragments (~0.5 kb to 5.0 kb) which melt apart more easily for the next step of labeling the DNA with radionucleotides. The DNA fragments were labeled by means of the hexamer random prime labeling method (Boehringer-Mannheim, Cat. #1004760). The labeled DNA was spermine precipitated (add 100 μl TE, 5 μl 0.1 M spermine, and 5 μl of 10 mg/ml salmon sperm DNA) to remove unincorporated radionucleotides. The labeled DNA was then resuspended in 100 μl TE, 0.5M NaCl at 65° C. for 5 minutes and then blocked with Human C_0t-1 DNA for 2–4 hrs. as per the manufacturer's instructions (Gibco/BRL, Cat. #5279SA). The C_0t-1 blocked probe was incubated on the filters in the blocking solution overnight at 42° C. The filters were washed for 30 minutes at room temperature in 2×SSC, 0.1% SDS, and then in the same buffer for 30 minutes at 55° C. The filters were then exposed 1 to 3 days at −70° C. to Kodak XAR-5 film with an intensifying screen. Thus, the blots were hybridized with either the pool of Eco-RI fragments from the insert, or each of the fragments individually.

The human DNA from clones in the region was isolated as whole insert or as EcoRI fragments and labeled as described above. The labeled DNA was used to screen filters of various cDNA libraries under the same conditions described above except that the cDNA filters undergo a more stringent wash of 0.1×SSC, 0.1% SDS at 65° C. for 30 minutes twice.

Most of the cDNA libraries used to date in our studies (libraries from normal breast tissue, breast tissue from a woman in her eighth month of pregnancy and a breast malignancy) were prepared at Clonetech, Inc. The cDNA library generated from breast tissue of an 8 month pregnant woman is available from Clonetech (Cat. #HL1037a) in the Lambda gt-10 vector, and is grown in C600Hfl bacterial host cells. Normal breast tissue and malignant breast tissue samples were isolated from a 37 year old Caucasian female and one-gram of each tissue was sent to Clonetech for mRNA processing and cDNA library construction. The latter two libraries were generated using both random and oligo-dT priming, with size selection of the final products which were then cloned into the Lambda Zap II vector, and grown in XL1-blue strain of bacteria as described by the manufacturer. Additional tissue-specific cDNA libraries include human fetal brain (Stratagene, Cat. 936206), human testis (Clonetech Cat. HL3024), human thymus (Clonetech Cat. HL 1127n), human brain (Clonetech Cat. HL11810), human placenta (Clonetech Cat 1075b), and human skeletal muscle (Clonetech Cat. HL1124b).

The cDNA libraries were plated with their host cells on NZCYM plates, and filter lifts are made in duplicate from each plate as per Maniatis et al. (1982). Insert (human) DNA from the candidate genomic clones was purified and radioactively labeled to high specific activity. The radioactive DNA was then hybridized to the cDNA filters to identify those cDNAs which correspond to genes located within the candidate cosmid clone. cDNAs identified by this method were picked, replated, and screened again with the labeled clone insert or its derived EcoRi fragment DNA to verify their positive status. Clones that were positive after this second round of screening were then grown up and their DNA purified for Southern blot analysis and sequencing. Clones were either purified as plasmid through in vivo excision of the plasmid from the Lambda vector as described in the protocols from the manufacturers, or isolated from the Lambda vector as a restriction fragment and subcloned into plasmid vector.

The Southern blot analysis was performed in duplicate, one using the original genomic insert DNA as a probe to verify that cDNA insert contains hybridizing sequences. The second blot was hybridized with cDNA insert DNA from the largest cDNA clone to identify which clones represent the same gene. All cDNAs which hybridize with the genomic clone and are unique were sequenced and the DNA analyzed to determine if the sequences represent known or unique genes. All cDNA clones which appear to be unique were further analyzed as candidate BRCA2 loci. Specifically, the clones are hybridized to Northern blots to look for breast specific expression and differential expression in normal versus breast tumor RNAs. They are also analyzed by PCR on clones in the BRCA2 region to verify their location. To map the extent of the locus, full length cDNAs are isolated and their sequences used as PCR probes on the YACs and the clones surrounding and including the original identifying clones. Intron-exon boundaries are then further defined through sequence analysis.

We have screened the normal breast, 8 month pregnant breast and fetal brain cDNA libraries with Eco RI fragments from cosmid BAC and P1 clones in the region. Potential BRCA2 cDNA clones were identified among the three libraries. Clones were picked, replated, and screened again with the original probe to verify that they were positive.

Analysis of hybrid-selected cDNA. cDNA fragments obtained from direct selection were checked by Southern blot hybridization against the probe DNA to verify that they originated from the contig. Those that passed this test were sequenced in their entirety. The set of DNA sequences obtained in this way were then checked against each other to find independent clones that overlapped.

The direct selection of cDNA method (Lovett et al., 1991; Futreal, 1993) is utilized with P1 and BAC DNA as the probe. The probe DNA is digested with a blunt cutting restriction enzyme such as HaeIII. Double-stranded adapters are then ligated onto the DNA and serve as binding sites for primers in subsequent PCR amplification reactions using biotinylated primers. Target cDNA is generated from mRNA derived from tissue samples, e.g., breast tissue, by synthesis of either random primed or oligo(dT) primed first strand, followed by second strand synthesis. The cDNA ends are rendered blunt and ligated onto double-stranded adapters. These adapters serve as amplification sites for PCR. The target and probe sequences are denatured and mixed with human C_0t-1 DNA to block repetitive sequences. Solution hybridization is carried out to high C_0t-½ values to ensure hybridization of rare target cDNA molecules. The annealed material is then captured on avidin beads, washed at high stringency and the retained cDNAs are eluted and amplified by PCR. The selected cDNA is subjected to further rounds of enrichment before cloning into a plasmid vector for analysis.

HTF island analysis. A method for identifying cosmids to use as probes on the cDNA libraries was HTF island analysis. HTF islands are segments of DNA which contain a very high frequency of unmethylated CpG dinucleotides (Tonolio et al., 1990) and are revealed by the clustering of restriction sites of enzymes whose recognition sequences include CpG dinucleotides. Enzymes known to be useful in HTF-island analysis are AscI, NotI, BssHII, EagI, SacII, NaeI, NarI, SmaI, and MluI (Anand, 1992).

Analysis of candidate clones. One or more of the candidate genes generated from above were sequenced and the information used for identification and classification of each expressed gene. The DNA sequences were compared to known genes by nucleotide sequence comparisons and by translation in all frames followed by a comparison with known amino acid sequences. This was accomplished using Genetic Data Environment (GDE) version 2.2 software and the Basic Local Alignment Search Tool (Blast) series of client-server software packages (e.g., BLASTN 1.3.13MP), for sequence comparison against both local and remote sequence databases (e.g., GenBank), running on Sun SPARC workstations. Sequences reconstructed from collections of cDNA clones identified with the cosmids and P1s have been generated. All candidate genes that represented new sequences were analyzed further to test their candidacy for the putative BRCA2 locus.

Mutation screening. To screen for mutations in the affected pedigrees, two different approaches were followed. First, genomic DNA isolated from family members known to carry the susceptibility allele of BRCA2 was used as a template for amplification of candidate gene sequences by PCR. If the PCR primers flank or overlap an intron/exon boundary, the amplified fragment will be larger than predicted from the cDNA sequence or will not be present in the amplified mixture. By a combination of such amplification experiments and sequencing of P1 or BAC clones using the set of designed primers it is possible to establish the intron/exon structure and ultimately obtain the DNA sequences of genomic DNA from the kindreds.

A second approach that is much more rapid if the intron/exon structure of the candidate gene is complex involves sequencing fragments amplified from cDNA synthesized from lymphocyte mRNA extracted from pedigree blood which was used as a substrate for PCR amplification using the set of designed primers. If the candidate gene is expressed to a significant extent in lymphocytes, such experiments usually produce amplified fragments that can be sequenced directly without knowledge of intron/exon junctions.

The products of such sequencing reactions were analyzed by gel electrophoresis to determine positions in the sequence that contain either mutations such as deletions or insertions, or base pair substitutions that cause amino acid changes or other detrimental effects.

Any sequence within the BRCA2 region that is expressed in breast is considered to be a candidate gene for BRCA2. Compelling evidence that a given candidate gene corresponds to BRCA2 comes from a demonstration that kindred families contain defective alleles of the candidate.

2. Specific Methods

Hybrid selection. Two distinct methods of hybrid selection were used in this work.

Method 1: cDNA preparation and selection. Randomly primed cDNA was prepared from poly $(A)^+$RNA of mammary gland, ovary testis, fetal brain and placenta tissues and from total RNA of the cell line Caco-2 (ATCC HTB 37). cDNAs were homopolymer tailed and then hybrid selected for two consecutive rounds of hybridization to immobilized P1 or BAC DNA as described previously. (Parimoo et al., 1991; Rommens et al., 1994). Groups of two to four overlapping P1 and/or BAC clones were used in individual selection experiments. Hybridizing cDNA was collected, passed over a G50 Fine Sephadex column and amplified using tailed primers. The products were then digested with EcoRI, size selected on agarose gels, and ligated into pBluescript (Stratagene) that had been digested with EcoRI and treated with calf alkaline phosphatase (Boehringer Mannheim). Ligation products were transformed into competent DH5α*E. coli* cells (Life Technologies, Inc.).

Characterization of Retrieved cDNAs. 200 to 300 individual colonies from each ligation (from each 250 kbases of genomic DNA) were picked and gridded into microtiter plates for ordering and storage. Cultures were replica transferred onto Hybond N membranes (Amersham) supported by LB agar with ampicillin. Colonies were allowed to propagate and were subsequently lysed with standard procedures. Initial analysis of the cDNA clones involved a prescreen for ribosomal sequences and subsequent cross screenings for detection of overlap and redundancy.

Approximately 10–25% of the clones were eliminated as they hybridized strongly with radiolabeled cDNA obtained from total RNA. Plasmids from 25 to 50 clones from each selection experiment that did not hybridize in prescreening were isolated for further analysis. The retrieved cDNA fragments were verified to originate from individual starting genomic clones by hybridization to restriction digests of DNAs of the starting clones, of a hamster hybrid cell line (GM10898A) that contains chromosome 13 as its only human material and to human genomic DNA. The clones were tentatively assigned into groups based on the overlapping or non-overlapping intervals of the genomic clones. Of the clones tested, approximately 85% mapped appropriately to the starting clones.

Method 2 (Lovett et al., 1991): cDNA Preparation. Poly (A) enriched RNA from human mammary gland, brain, lymphocyte and stomach were reverse-transcribed using the tailed random primer XN$_{12}$

[5'-(NH$_2$)-GTAGTGCAAGGCTCGAGAACNNNNN-NNNNNNN] (SEQ ID NO:3) and Superscript II reverse transcriptase (Gibco BRL). After second strand synthesis and end polishing, the ds cDNA was purified on Sepharose CL-4B columns (Pharmacia). cDNAs were "anchored" by ligation of a double-stranded oligo RP

[5'-(NH$_2$)-TGAGTAGAATTCTAACGGCCGTC-ATTGTTC (SEQ ID NO:4) annealed to

5'-GAACAATGACGGCCGTTAGAATTCTACTCA-(NH$_2$) (SEQ ID NO:5)] to their 5' ends (5' relative to mRNA) using T4 DNA ligase. Anchored ds cDNA was then repurified on Sepharose CL-4B columns.

Selection. cDNAs from mammary gland, brain, lymphocyte and stomach tissues were first amplified using a nested version of RP

(RP.A: 5'-TGAGTAGAATTCTAACGGCCGTCAT) (SEQ ID NO:6) and

XPCR [5'-(PO$_4$)-GTAGTGCAAGGCTCGAGAAC (SEQ ID NO:7)] and purified by fractionation on Sepharose CL-4B. Selection probes were prepared from purified P1s, BACs or PACs by digestion with HinfI and Exonuclease III. The single-stranded probe was photolabelled with photobiotin (Gibco BRL) according to the manufacturer's recommendations. Probe, cDNA and Cot-1 DNA were hybridized in 2.4M TEA-CL, 10 mM NaPO$_4$, 1 mM EDTA. Hybridized cDNAs were captured on streptavidin-paramagnetic particles (Dynal), eluted, reamplified with a further nested version of RP

[RP.B: 5'-(PO$_4$)-TGAGTAGAATTCTAACGGCCGT-CATTG (SEQ ID NO:8)] and XPCR, and size-selected on Sepharose CL-6B. The selected, amplified cDNA was hybridized with an additional aliquot of probe and C$_0$t-1 DNA. Captured and eluted products were amplified again with RP.B and XPCR, size-selected by gel electrophoresis and cloned into dephosphorylated HincII cut pUC18. Ligation products were transformed into XL2-Blue ultracompetent cells (Stratagene).

Analysis. Approximately 192 colonies for each single-probe selection experiment were amplified by colony PCR using vector primers and blotted in duplicate onto Zeta Probe nylon filters (Bio-Rad). The filters were hybridized using standard procedures with either random primed C$_0$t-1 DNA or probe DNA (P1, BAC or PAC). Probe-positive, C$_0$t-1 negative clones were sequenced in both directions using vector primers on an ABI 377sequencer.

Exon Trapping. Exon amplification was performed using a minimally overlapping set of BACs, P1s and PACs in order to isolate a number of gene sequences from the BRCA2 candidate region. Pools of genomic clones were assembled, containing from 100–300 kb of DNA in the form of 1–3 overlapping genomic clones. Genomic clones were digested with PstI or BamHI+ BglII and ligated into PstI or BamHI sites of the pSPL3 splicing vector. The exon amplification technique was performed (Church et al., 1993) and the end products were cloned in the pAMP1 plasmid from the Uracil DNA Glycosylase cloning system (BRL). Approximately 6000 clones were picked, propagated in 96 well plates, stamped onto filters, and analyzed for the presence of vector and repeat sequences by hybridization. Each clone insert was PCR amplified and tested for redundancy, localization and human specificity by hybridization to grids of exons and dot blots of the parent genomic DNA. Unique candidate exons were sequenced, searched against the databases, and used for hybridization to cDNA libraries.

5' RACE. The 5' end of BRCA2 was identified by a modified RACE protocol called biotin capture RACE. Poly (A) enriched RNA from human mammary gland and thymus was reverse-transcribed using the tailed random primer XN$_{12}$

[5' (NH$_2$)-GTAGTGCAAGGCTCGAGAACNNNN (SEQ ID NO:3)] and Superscript II reverse transcriptase (Gibco BRL). The RNA strand was hydrolyzed in NaOH and first strand cDNA purified by fractionation on Sepharose CL-4B (Pharmacia). First strand cDNAs were "anchored" by ligation of a double-stranded oligo with a 7 bp random 5' overhang [ds UCA: 5'-CCTTCACACGCGTATCGATTA-GTCACNNNNNNN-(NH$_2$) (SEQ ID NO:9) annealed to 5'-(PO$_4$)-GTGACTAATCGATACGCGTGTGAAGGTGC (SEQ ID NO:10)] to their 3' ends using T4 DNA ligase. After ligation, the anchored cDNA was repurified by fractionation on Sepharose CL-4B. The 5' end of BRCA2 was amplified using a biotinylated reverse primer [5'-(B)-TTGAAGAACAACAGGACTTTCACTA] (SEQ ID NO:11) and a nested version of UCA [UCP.A: 5'-CACCTTCACACGCGTATCG (SEQ ID NO:12)]. PCR products were fractionated on an agarose gel, gel purified, and captured on streptavidin-paramagnetic particles (Dynal). Captured cDNA was reamplified using a nested reverse primer [5'-GTTCGTAATTGTTGTTTTTATGTT-CAG](SEQ ID NO: 13) and a further nested version of UCA [UCP.B: 5'-CCTTTCACACGCGTATCGATTAG] (SEQ ID NO:14)]. This PCR reaction gave a single sharp band on an agarose gel; the DNA was gel purified and sequenced in both directions on an ABI 377 sequencer.

cDNA Clones. Human cDNA libraries were screened with ^{32}P-labeled hybrid selected or exon trapped clones. Phage eluted from tertiary plaques were PCR amplified with vector-specific primers and then sequenced on an ABI 377sequencer.

Northern Blots. Multiple Tissue Northern (MTN) filters, which are loaded with 2 μg per lane of poly(A)+ RNA derived from a number of human tissues, were purchased from Clonetech. ^{32}P-random-primer labeled probes corresponding to retrieved cDNAs GT 713 (BRCA2 exons 3–7), λ wCPF1B8.1 (3α end of exon 11 into exon 20), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were used to probe the filters. Prehybridizations were at 42° C. in 50% formamide, 5× SSPE, 1% SDS, 5× Denhardt's mixture, 0.2 mg/ml denatured salmon testis DNA and 2 μg/ml poly (A). Hybridizations were in the same solution with the addition of dextran sulfate to 4% and probe. Stringency washes were in 0.1×SSC/0.1% SDS at 50° C.

RT-PCR Analysis. Ten μg of total RNA extracted from five human breast cancer cell lines (ZR-75-1, T-47D, MDA-MB-231, MDA-MB468 and BT-20) and three human prostate cancer cell lines (LNCaP, DU145 and PC-3) (RNAs provided by Dr. Claude Labrie, CHUL Research Center) were reverse transcribed using the primer mH20-1D05#RA

[5'-TTTGGATCATTTTCACACTGTC] (SEQ ID NO:15)] and Superscript II reverse transcriptase (Gibco BRL). Thereafter, the single strand cDNAs were amplified using the primers CG026#FB

[5'-GTGCTCATAGTCAGAAATGAAG] (SEQ ID NO:16)] and mH20-1*D05*#RA (this is the primer pair that was used to island hop from the exon 7/8 junction into exon

11; the PCR product is about 1.55 kb). PCR products were fractionated on a 1.2% agarose gel.

PCR Amplification and Mutation Screening. All 26 coding exons of BRCA2 and their associated splice sites were amplified from genomic DNA as described (Kamb et al., 1994b). The DNA sequences of the primers, some of which lie in flanking intron sequence, used for amplification and sequencing appear in Table 2. Some of the exons (2 through 10, 11-5, 11-6, 11-7 and 23 through 27) were amplified by a simple one-step method. The PCR conditions for those exons were: single denaturing step of 95° C. (1 min.); 40 cycles of 96° C. (6sec.), T_{ann}=55° C. (15sec.), 72° C. (1 min.) Other exons (11–22) required nested reamplification after the primary PCR reaction. In these cases, the initial amplification was carried out with the primers in the first two columns of Table 2 for 19 cycles as described above. Nested reamplification for these exons was carried out for 28 or 32 cycles at the same conditions with the primers appearing in the third column of Table 2. The buffer conditions were as described (Kamb et al., 1994b). The products were purified from 0.8% agarose gels using Qiaex beads (Qiagen). The purified products were analyzed by cycle sequencing with α-P^{32}dATP with Ampli-Cycle™ Sequencing Kit (Perkin Elmer, Branchburg, N.J.). The reaction products were fractionated on 6% polyacrylamide gels. All (A) reactions were loaded adjacent each other, followed by the (C) reactions, etc. Detection of polymorphisms was carried out visually and confirmed on the other strand.

TABLE 2

Primers for Amplifying BRCA2 Exons

EXON	FORWARD PRIMER	REVERSE PRIMER	NESTED PRIMER
2	TGTTCCCATCCTCACAGTAAG$^{*(17)}$	GTACTGGGTTTTTAGCAAGCA$^{*(18)}$	
3	GGTTAAAACTAAGGTGGGA$^{*(19)}$	ATTTGCCCAGCATGACACA*(20)	
4	TTTCCCAGTATAGAGGAGA$^{*(21)}$	GTAGGAAAATGTTTCATTTAA*(22)	
5	ATCTAAAGTAGTATTCCAACA$^{*(23)}$	GGGGGTAAAAAAAGGGGAA$^{*(24)}$	
6	GAGATAAGTCAGGTATGATT$^{*(25)}$	AATTGCCTGTATGAGGCAGA$^{*(26)}$	
7	GGCAATTCAGTAAACGTTAA$^{*(27)}$	ATTGTCAGTTACTAACACAC$^{*(28)}$	
8	GTGTCATGTAATCAAATAGT$^{*(29)}$	CAGGTTTAGAGACTTTCTC$^{*(30)}$	
9	GGACCTAGGTTGATTGCA$^{*(31)}$	GTCAAGAAAGGTAAGGTAA$^{*(32)}$	
10-1	CTATGAGAAAGGTTGTGAG$^{*(33)}$	CCTAGTCTTGCTAGTTCTT$^{*(34)}$	
10-2	AACAGTTGTAGATACCTCTGAA$^{*(35)}$	GACTTTTTGATACCCTGAAATG$^{*(36)}$	
10-3	CAGCATCTTGAATCTCATACAG$^{*(37)}$	CATGTATACAGATGATGCCTAAG$^{*(38)}$	
11-1	AACTTAGTGAAAAATATTTAGTGA$^{(39)}$	ATACATCTTGATTCTTTTCCAT$^{*(40)}$	TTTAGTGAATGTGATTGATGGT$^{*(41)}$
11-2	AGAACCAACTTTGTCCTTAA$^{(42)}$	TTAGATTTGTGTTTTGGTTGAA$^{*(43)}$	TAGCTCTTTTGGGACAATTC$^{*(44)}$
11-3	ATGGAAAAGAATCAAGATGTAT$^{*(45)}$	CCTAATGTTATGTTCAGAGAG$^{(46)}$	GCTACCTCCAAAACTGTGA$^{*(47)}$
11-4	GTGTAAAGCAGCATATAAAAAT$^{*(48)}$	CTTGCTGCTGTCTACCTG$^{(49)}$	AGTGGTCTTAAGATAGTCAT$^{*(50)}$
11-5	CCATAATTTAACACCTAGCCA$^{**(51)}$	CCAAAAAAGTTAAATCTGACA$^{**(52)}$	
	GGCTTTTATTCTGCTCATGGC$^{*(53)}$	CCTCTGCAGAAGTTTCCTCAC$^{*(54)}$	
11-6	AACGGACTTGCTATTTACTGA$^{*(55)}$	AGTACCTTGCTCTTTTTCATC$^{*(56)}$	
11-7	CAGCTAGCGGGAAAAAAGTTA$^{*(57)}$	TTCGGAGAGATGATTTTTGTC$^{*(58)}$	
11-8	GCCTTAGCTTTTTACACAA$^{*(59)}$	TTTTTGATTATATCTCGTTG$^{(60)}$	TTATTCTCGTTGTTTTCCTTA$^{*(61)}$
11-9	CCATTAAATTGTCCATATCTA$^{*(62)}$	GACGTAGGTGAATAGTGAAGA$^{(63)}$	TCAAATTCCTCTAACACTCC$^{*(64)}$
11-10	GAAGATAGTACCAAGCAAGTC$^{(65)}$	TGAGACTTTGGTTCCTAATAC$^{*(66)}$	AGTAACGAACATTCAGACCAG$^{*(67)}$
11-11	GTCTTCACTATTCACCTACG$^{*(68)}$	CCCCCAAACTGACTACACAA$^{(69)}$	AGCATACCAAGTCTACTGAAT$^{*(70)}$
12	ACTCTTTCAAACATTAGGTCA$^{*(71)}$	TTGGAGAGGCAGGTGGAT$^{(72)}$	CTATAGAGGGAGAACAGAT$^{*(73)}$
13	TTTATGCTGATTTCTGTTGTAT$^{(74)}$	ATAAAACGGGAAGTGTTAACT$^{*(75)}$	CTGTGAGTTATTTGGTGCAT$^{*(76)}$
14	GAATACAAAACAGTTACCAGA$^{(77)}$	CACCACCAAAGGGGGAAA$^{*(78)}$	AAATGAGGGTCTGCAACAAA$^{*(79)}$
15	GTCCGACCAGAACTTGAG$^{(80)}$	AGCCATTTGTAGGATACTAG$^{*(81)}$	CTACTAGACGGGCGGAG$^{*(82)}$
16	ATGTTTTTGTAGTGAAGATTCT$^{(83)}$	TAGTTCGAGAGACAGTTAAG$^{*(84)}$	CAGTTTTGGTTTGTTATAATTG$^{*(85)}$
17	CAGAGAATAGTTGTAGTTGTT$^{(86)}$	AACCTTAACCCATACTGCC$^{*(87)}$	TTCAGTATCATCCTATGTGG$^{*(88)}$
18	TTTTATTCTCAGTTATTCAGTG$^{(89)}$	GAAATTGAGCATCCTTAGTAA$^{*(90)}$	AATTCTAGAGTCACACTTCC$^{*(91)}$
19	ATATTTTTAAGGCAGTTCTAGA$^{(92)}$	TTACACACACCAAAAAAGTCA$^{*(93)}$	TGAAAACTCTTATGATATCTGT$^{*(94)}$
20	TGAATGTTATATATGTGACTTTT$^{*(95)}$	CTTGTTGCTATTCTTTGTCTA$^{(96)}$	CCCTAGATACTAAAAAATAAAG$^{*(97)}$
21	CTTTTAGCAGTTATATAGTTTC$^{(98)}$	GCCAGAGAGTCTAAAACAG$^{*(99)}$	CTTTGGGTGTTTTATGCTTG$^{*(100)}$
22	TTTGTTGTATTTGTCCTGTTTA$^{(101)}$	ATTTTGTTAGTAAGGTCATTTTT$^{*(102)}$	GTTCTGATTGCTTTTTATTCC$^{*(103)}$
23	ATCACTTCTTCCATTGCATC$^{*(104)}$	CCGTGGCTGGTAAATCTG$^{*(105)}$	
24	CTGGTAGCTCCAACTAATC$^{*(106)}$	ACCGGTACAAACCTTTCATTG$^{*(107)}$	
25	CTATTTTGATTTGCTTTTATTATT$^{*(108)}$	GCTATTTCCTTGATACTGGAC$^{*(109)}$	
26	TTGGAAACATAAATATGTGGG$^{*(110)}$	ACTTACAGGAGCCACATAAC$^{*(111)}$	
27	CTACATTAATTATGATAGGCTNCG$^{**(112)}$	GTACTAATGTGTGGTTTGAAA$^{**(113)}$ TCAATGCAAGTTCTTCGTCAGC$^{*(114)}$	

Primers with an "*" were used for sequencing.
Primers without an "*" were replaced by the internal nested primer for both the second round of PCR and sequencing.
For large exons requiring internal sequencing primers, primers with an "**" were used to amplify the exon.
Number in parathensis referes to the SEQ ID NO: for each primer.

EXAMPLE 4

Identification of BRCA2

Assembly of the full-length BRCA2sequence. The full-length sequence of BRCA2 was assembled by combination of several smaller sequences obtained from hybrid selection, exon trapping, cDNA library screening, genomic sequencing, and PCR experiments using cDNA as template for amplification (i.e., "island hopping") (FIG. 2). The extreme 5' end of the mRNA including the predicted translational start site was identified by a modified 5' RACE protocol (Stone et al., 1995). The first nucleotide in the sequence (nucleotide 1) is a non-template G, an indication that the mRNA cap is contained in the sequence. One of the exons (exon 11) located on the interior of the BRCA2 cDNA is nearly 5 kb. A portion of exon 11 was identified by analysis of roughly 900 kb of genomic sequence in the public domain (ftp://genome.wustl.edu/pub/gsc1/brca).

This genomic sequence was condensed with genomic sequence determined by us into a set of 160 sequence contigs. When the condensed genomic sequence was scanned for open reading frames (ORFs), a contiguous stretch of nearly 5 kb was identified that was spanned by long ORFs. This sequence was linked together by island hopping experiments with two previously identified candidate gene fragments. The current composite BRCA2 cDNA sequence consists of 11,385 bp, but does not include the polyadenylation signal or poly(A) tail. This cDNA sequence is set forth in SEQ ID NO:1 and FIG. 3.

Structure of the BRCA2 gene and BRCA2 polypeptide. Conceptual translation of the cDNA revealed an ORF that began at nucleotide 229 and encoded a predicted protein of 3418 amino acids. The peptide bears no discernible similarity to other proteins apart from sequence composition. There is no signal sequence at the amino terminus, and no obvious membrane- spanning regions. Like BRCA1, the BRCA2 protein is highly charged. Roughly one quarter of the residues are acidic or basic.

The BRCA2 gene structure was determined by comparison of cDNA and genomic sequences. BRCA2 is composed of 27 exons distributed over roughly 70 kb of genomic DNA. A CpG-rich region at the 5' end of BRCA2 extending upstream suggests the presence of regulatory signals often associated with CpG "islands." Based on Southern blot experiments, BRCA2 appears to be unique, with no close homologs in the human genome.

Expression studies of BRCA2. Hybridization of labeled cDNA to human multiple tissue Northern filters revealed an 11–12 kb transcript that was detectable in testis only. The size of the this transcript suggests that little of the BRCA2 mRNA sequence is missing from our composite cDNA. Because the Northern filters did not include mammary gland RNA, RT-PCR experiments using a BRCA2 cDNA amplicon were performed on five breast and three prostate cancer cell line RNAs. All of the lines produced positive signals. In addition, PCR of a BRCA2 amplicon (1-BrCG026→5kb) and 5' RACE were used to compare mammary gland and thymus cDNA as templates for amplification. In both cases, the product amplified more efficiently from breast than from thymus.

Germline mutations in BRCA2. Individuals from eighteen putative BRCA2 kindreds were screened for BRCA2 germline mutations by DNA sequence analysis (Wooster et al., 1994). Twelve kindreds have at least one case of male breast cancer, four have two or more cases; and, four include at least one individual affected with ovarian cancer who shares the linked BRCA2 haplotype. Each of the 18 kindreds has a posterior probability of harboring a BRCA2 mutation of at least 69%, and nine kindreds have posterior probabilities greater than 90%. Based on these combined probabilities, 16 of 18 kindreds are expected to segregate BRCA2 mutations. The entire coding sequence and associated splice junctions were screened for mutations in multiple individuals from nine kindreds using either cDNA or genomic DNA (Table 3). Individuals from the remaining nine kindreds were screened for mutations using only genomic DNA. These latter screening experiments encompassed 99% of the coding sequence (all exons excluding exon 15) and all but two of the splice junctions.

Sequence alterations were identified in 9 of 18 kindreds. All except one involved nucleotide deletions that altered the reading frame, leading to truncation of the predicted BRCA2 protein. The single exception contained a deletion of three nucleotides (kindred 1019). All nine mutations differed from one another.

A subset of kindreds was tested for transcript loss. cDNA samples were available for a group of nine kindreds, but three of the nine kindreds in the group contained frameshift mutations. Specific polymorphic sites know to be heterozygous in genomic DNA were examined in cDNA from

TABLE 3

							Set of Families Screened for BRCA2 Mutations			
Family	FBC	FBC <50 yrs	Ov	MBC	LOD	Prior Probability	BRCA2 Mutation	Exon	Codon	Effect
UT-107^1	20	18	2	3	5.06	1.00	277 delAC	2	17	termination codon at 29
UT-1018^1	11	9	0	1	2.47	1.00	982 del4	9	252	termination codon at 275
UT-2044^1	8	6	4	1	2.13	1.00	4706 del4	11	1493	termination codon at 1502
UT-2367^1	6	5	1	0	2.09	0.99	IR			
UT-2327^1	13	6	0	0	1.92	0.99	ND			
UT-2388^1	3	3	1	0	0.92	0.92	ND			
UT-2328^1	10	4	0	1	0.21	0.87	ND			
UT-4328^1	4	3	0	0	0.18	0.69	ND			
MI-1016^1	4	2	0	1	0.04	0.81	ND			
CU-20^2	4	3	2	2	1.09	1.00	8525 delC	18	2766	termination codon at 2776
CU-1592^2	8	4	0	0	0.99	0.94	9254 del5	23	3009	termination codon at 3015
UT-2043^2	2	2	1	1	0.86	0.97	4075 delGT	11	1283	termination codon at 1285
IC-2204^2	3	1	0	4	0.51	0.98	999 del5	9	257	termination codon at 273
MS-075^2	4	1	0	1	0.50	0.93	6174 delT	11	1982	termination codon at 2003
UT-1019^2	5	1	0	2	nd	0.95	4132 del3	11	1302	deletion of thr_{1302}
UT-2022^2	4	4	0	1	0.39	0.79	ND			
UT-2263^2	3	2	0	1	nd	0.9	ND			
UT-2171^2	5	4	2	0	nd	nd	ND			

[1] Families screened for complete coding sequence and with informative cDNA sample.

[2] Families screened for all BRCA2 exons except 15 and for which there was no informative cDNA sample available.

IR - inferred regulatory mutation

nd - not determined

Ov - Ovarian Cancer

ND - none detected

FBC - Female Breast Cancer

MBC - Male Breast Cancer

kindred individuals. The appearance of hemizygosity at these polymorphic sites was interpreted as evidence for a mutation leading to reduction in mRNA levels. In only one of the six cases with no detectable sequence alteration (kindred 2367) could such a regulatory mutation be inferred. In addition, one of the three kindreds with a frameshift mutation (kindred 2044) displayed signs of transcript loss. This implies that some mutations in the BRCA2 coding sequence may destabilize the transcript in addition to disrupting the protein sequence. Such mutations have been observed in BRCA1 (Friedman et al., 1995). Thus, 56% of the kindreds (10 of 18) contained an altered BRCA2 gene.

Role of BRCA2 in Cancer. Most tumor suppressor genes identified to date give rise to protein products that are absent, nonfunctional, or reduced in function. The majority of TP53 mutations are missense; some of these have been shown to produce abnormal p53 molecules that interfere with the function of the wildtype product (Shaulian et al., 1992; Srivastava et al., 1993). A similar dominant negative mechanism of action has been proposed for some adenomatous polyposis coli (APC) alleles that produce truncated molecules (Su et al., 1993), and for point mutations in the Wilms' tumor gene (WT1) that alter DNA binding of the protein (Little et al., 1993). The nature of the mutations observed in the BRCA2 coding sequence is consistent with production of either dominant negative proteins or nonfunctional proteins.

EXAMPLE 5

Analysis of the BRCA2 Gene

The structure and function of BRCA2 gene are determined according to the following methods.

Biological Studies. Mammalian expression vectors containing BRCA2 cDNA are constructed and transfected into appropriate breast carcinoma cells with lesions in the gene. Wild-type BRCA2 cDNA as well as altered BRCA2 cDNA are utilized. The altered BRCA2 cDNA can be obtained from altered BRCA2 alleles or produced as described below. Phenotypic reversion in cultures (e.g., cell morphology, doubling time, anchorage-independent growth) and in animals (e.g., tumorigenicity) is examined. The studies will employ both wild-type and mutant forms (Section B) of the gene.

Molecular Genetics Studies. In vitro mutagenesis is performed to construct deletion mutants and missense mutants (by single base-pair substitutions in individual codons and cluster charged → alanine scanning mutagenesis). The mutants are used in biological, biochemical and biophysical studies.

Mechanism Studies. The ability of BRCA2 protein to bind to known and unknown DNA sequences is examined. Its ability to transactivate promoters is analyzed by transient reporter expression systems in mammalian cells. Conventional procedures such as particle-capture and yeast two-hybrid system are used to discover and identify any functional partners. The nature and functions of the partners are characterized. These partners in turn are targets for drug discovery.

Structural Studies. Recombinant proteins are produced in *E. coli*, yeast, insect and/or mammalian cells and are used in crystallographical and NMR studies. Molecular modeling of the proteins is also employed. These studies facilitate structure-driven drug design.

EXAMPLE 6

Two Step Assay to Detect the Presence of BRCA2 in a Sample

Patient sample is processed according to the method disclosed by Antonarakis et al. (1985), separated through a 1% agarose gel and transferred to nylon membrane for Southern blot analysis. Membranes are UV cross linked at 150 mJ using a GS Gene Linker (Bio-Rad). A BRCA2 probe selected from the sequence shown in FIG. 3 is subcloned into pTZ18U. The phagemids are transformed into E. coli MV1190 infected with M13KO7 helper phage (Bio-Rad, Richmond, Calif.). Single stranded DNA is isolated according to standard procedures (see Sambrook et al., 1989).

Blots are prehybridized for 15–30 min at 65° C. in 7% sodium dodecyl sulfate (SDS) in 0.5M $NaPO_4$. The methods follow those described by Nguyen et al., 1992. The blots are hybridized overnight at 65° C. in 7% SDS, 0.5M $NaPO_4$ with 25–50 ng/ml single stranded probe DNA. Post-hybridization washes consist of two 30 min washes in 5% SDS, 40 mM $NaPO_4$ at 65° C., followed by two 30 min washes in 1% SDS, 40 mM $NaPO_4$ at 65° C.

Next the blots are rinsed with phosphate buffered saline (pH 6.8) for 5 min at room temperature and incubated with 0.2% casein in PBS for 30–60 min at room temperature and rinsed in PBS for 5 min. The blots are then preincubated for 5–10 minutes in a shaking water bath at 45° C. with hybridization buffer consisting of 6M urea, 0.3M NaCl, and 5× Denhardt's solution (see Sambrook, et al., 1989). The buffer is removed and replaced with 50–75 $\mu l/cm^2$ fresh hybridization buffer plus 2.5 nM of the covalently cross-linked oligonucleotide-alkaline phosphatase conjugate with the nucleotide sequence complementary to the universal primer site (UP-AP, Bio-Rad). The blots are hybridized for 20–30 min at 45° C. and post hybridization washes are incubated at 45° C. as two 10 min washes in 6M urea, 1× standard saline citrate (SSC), 0.1% SDS and one 10 min wash in 1× SSC, 0.1% Triton®X-100. The blots are rinsed for 10 min at room temperature with 1× SSC.

Blots are incubated for 10 min at room temperature with shaking in the substrate buffer consisting of 0.1M diethanolamine, 1 mM $MgCl_2$, 0.02% sodium azide, pH 10.0. Individual blots are placed in heat sealable bags with substrate buffer and 0.2 mM AMPPD (3-(2'-spiroadamantane)-4-methoxy-4-(3'-phosphoryloxy)phenyl-1,2-dioxetane, disodium salt, Bio-Rad). After a 20 min incubation at room temperature with shaking, the excess AMPPD solution is removed. The blot is exposed to X-ray film overnight. Positive bands indicate the presence of BRCA2.

EXAMPLE 7

Generation of Polyclonal Antibody against BRCA2

Segments of BRCA2 coding sequence are expressed as fusion protein in *E. coli*. The overexpressed protein is purified by gel elution and used to immunize rabbits and mice using a procedure similar to the one described by Harlow and Lane, 1988. This procedure has been shown to generate Abs against various other proteins (for example, see Kraemer et al., 1993).

Briefly, a stretch of BRCA2 coding sequence selected from the sequence shown in FIG. 3 is cloned as a fusion protein in plasmid PET5A (Novagen, Inc., Madison, Wis.). After induction with IPTG, the overexpression of a fusion protein with the expected molecular weight is verified by SDS/PAGE. Fusion protein is purified from the gel by electroelution. The identification of the protein as the BRCA2 fusion product is verified by protein sequencing at the N-terminus. Next, the purified protein is used as immunogen in rabbits. Rabbits are immunized with 100 μg of the protein in complete Freund's adjuvant and boosted twice in

3 week intervals, first with 100 μg of immunogen in incomplete Freund's adjuvant followed by 100 μg of immunogen in PBS. Antibody containing serum is collected two weeks thereafter.

This procedure is repeated to generate antibodies against the mutant forms of the BRCA2 gene. These antibodies, in conjunction with antibodies to wild type BRCA2, are used to detect the presence and the relative level of the mutant forms in various tissues and biological fluids.

EXAMPLE 8

Generation of Monoclonal Antibodies Specific for BRCA2

Monoclonal antibodies are generated according to the following protocol. Mice are immunized with immunogen comprising intact BRCA2 or BRCA2 peptides (wild type or mutant) conjugated to keyhole limpet hemocyanin using glutaraldehyde or EDC as is well known.

The immunogen is mixed with an adjuvant. Each mouse receives four injections of 10 to 100 μg of immunogen and after the fourth injection blood samples are taken from the mice to determine if the serum contains antibody to the immunogen. Serum titer is determined by ELISA or RIA. Mice with sera indicating the presence of antibody to the immunogen are selected for hybridoma production.

Spleens are removed from immune mice and a single cell suspension is prepared (see Harlow and Lane, 1988). Cell fusions are performed essentially as described by Kohler and Milstein, 1975. Briefly, P3.65.3 myeloma cells (American Type Culture Collection, Rockville, MD) are fused with immune spleen cells using polyethylene glycol as described by Harlow and Lane, 1988. Cells are plated at a density of 2×10^5 cells/well in 96 well tissue culture plates. Individual wells are examined for growth and the supernatants of wells with growth are tested for the presence of BRCA2specific antibodies by ELISA or RIA using wild type or mutant BRCA2 target protein. Cells in positive wells are expanded and subcloned to establish and confirm monoclonality.

Clones with the desired specificities are expanded and grown as ascites in mice or in a hollow fiber system to produce sufficient quantities of antibody for characterization and assay development.

EXAMPLE 9

Sandwich Assay for BRCA2

Monoclonal antibody is attached to a solid surface such as a plate, tube, bead, or particle. Preferably, the antibody is attached to the well surface of a 96-well ELISA plate. 100 μl sample (e.g., serum, urine, tissue cytosol) containing the BRCA2 peptide/protein (wild-type or mutant) is added to the solid phase antibody. The sample is incubated for 2 hrs at room temperature. Next the sample fluid is decanted, and the solid phase is washed with buffer to remove unbound material. 100 μl of a second monoclonal antibody (to a different determinant on the BRCA2 peptide/protein) is added to the solid phase. This antibody is labeled with a detector molecule (e.g., ^{125}I, enzyme, fluorophore, or a chromophore) and the solid phase with the second antibody is incubated for two hrs at room temperature. The second antibody is decanted and the solid phase is washed with buffer to remove unbound material.

The amount of bound label, which is proportional to the amount of BRCA2 peptide/protein present in the sample, is quantitated. Separate assays are performed using monoclonal antibodies which are specific for the wild-type BRCA2 as well as monoclonal antibodies specific for each of the mutations identified in BRCA2.

EXAMPLE 10

The 6174delT Mutation is Common in Ashkenazi Jewish Women Affected by Breast Cancer

The 6174delT mutation (see Table 3) has been found to be present in many cases of Ashkenazi Jewish women who have had breast cancer (Neuhausen et al., 1996). Two groups of probands comprised the ascertainment for this study. The first group was ascertained based on both age-of-onset and a positive family history. The first group consisted of probands affected with breast cancer on or before 41 years of age with or without a family history of breast cancer. Inclusion criteria for the second group were that the proband was affected with breast cancer between the ages of 41 and 51 with one or more first degree relatives affected with breast or ovarian cancer on or before the age of 50; or the proband was affected with breast cancer between the ages of 41 and 51 with two or more second degree relatives affected with breast or ovarian cancer, 1 on or before age 50; or the proband was affected between the ages of 41 and 51 with both primary breast and primary ovarian cancer. Probands were ascertained through medical oncology and genetic counseling clinics, with an effort to offer study participation to all eligible patients. Family history was obtained by a self-report questionnaire. Histologic confirmation of diagnosis was obtained for probands in all cases. Religious background was confirmed on all probands by self report or interview.

Mutation Detection

The BRCA2 6174delT mutation was detected by amplifying genomic DNA from each patient according to standard polymerase chain reaction (PCR) procedures (Saiki et al., 1985; Mullis et al., 1986; Weber and May, 1989). The primers used for the PCR are:

BC11-RP: GGGAAGCTTCATAAGTCAGTC (SEQ ID NO: 115) (forward primer) and

BC11-LP: TTTGTAATGAAGCATCTGATACC (SEQ ID NO: 116) (reverse primer).

The reactions were performed in a total volume of 10.0 μl containing 20 ng DNA with annealing at 55° C. This produces a PCR product 97 bp long in wild-type samples and 96 bp long when the 6174delT mutation is present. The radiolabeled PCR products were electrophoresed on standard 6% polyacrylamide denaturing sequencing gels at 65W for 2 hours. The gels were then dried and autoradiographed. All the cases exhibiting the 1 bp deletion were sequenced to confirm the 6174delT mutation. For sequencing, half of the samples were amplified with one set of PCR primers and the coding strand was sequenced and the other half of the samples were amplified with a second set of PCR primers and the noncoding strand was sequenced. For one set the PCR primers were:

TD-SFB: AATGATGAATGTAGCACGC (SEQ ID NO: 117) (forward primer) and

CGORF-RH: GTCTGAATGTTCGTTACT (SEQ ID NO: 118) (reverse primer).

This results in an amplified product of 342 bp in wild-type and 341 bp for samples containing the 6174delT mutation. For this set of samples the amplified DNA was sequenced using the CGORF-RH primer for the sequencing primer. The other half of the samples were amplified using the BC11-RP forward primer and the CGORF-RH reverse primer resulting in a fragment of 183 bp in wild-type samples and 182 bp in samples containing the 6174delT mutation. This was sequenced using BC11-RP as the sequencing primer.

Results

Six out of eighty women of Ashkenazi Jewish ancestry with breast cancer before the age of 42 had the 6174delT mutation. This compares to zero cases of the mutation being present in a control group of non-Jewish women who had breast cancer before the age of 42. These cases were ascertained without regard to family history. Table 4shows the results of the study. Four of the six cases with the 6174delT mutation had a family history of breast or ovarian cancer in a first or second degree relative. In each of two kindreds where multiple samples were available for analysis, the 6174delT mutation co-segregated with two or more cases of breast or ovarian cancer. A second cohort of 27 Ashkenazim with breast cancer at age 42–50 and a history of at least one additional relative affected with breast or ovarian cancer provided an additional estimate of the frequency of the 6174delT mutation. In this group of 27 women, two were heterozygous for the BRCA2 6174delT mutation. One of these individuals had first degree relatives with both ovarian and breast cancer. From the data presented, and assuming a penetrance similar to BRCA1 mutations (Offit et al., 1996; Langston et al., 1996), the frequency of the 6174delT mutation in Ashkenazim can be estimated to be approximately 3 per thousand. However, if the penetrance of this mutation is lower than BRCA1, then the frequency of this mutation will be higher. A more precise estimate of the carrier frequency of the 6174delT mutation in individuals of Ashkenazi Jewish ancestry will emerge from large-scale population studies.

TABLE 4

Group	Number of subjects tested, n=	Number with 6174delT, n=	%
Group 1a			
Diagnosis before age 42, Non-Jewish^a	93	0	(0)
Group 1b			
Diagnosis before age 42, Jewish^a	80	6	(8)
Before age 37	40	4	(10)
age 37–41	40	2	(5)
Group 2			
Diagnosis ages 42–50 and family history positive^b	27	2	(27)

Key:

^{a}- Ascertained regardless of family history

^{b}- Family history for this group was defined as one first degree or two second degree relatives diagnosed with breast or ovarian cancer, one before age 50.

EXAMPLE 11

BRCA2 Shows a Low Somatic Mutation Rate in Breast Carcinoma and Other Cancers Including Ovarian and Pancreatic Cancers

BRCA2 is a tumor suppressor gene. A homozygous deletion of this gene may lead to breast cancer as well as other cancers. A homozygous deletion in a pancreatic xenograft was instrumental in the effort to isolate BRCA2 by positional cloning. Cancer may also result if there is a loss of one BRCA2 allele and a mutation in the remaining allele (loss of heterozygosity or LOH). Mutations in both alleles may also lead to development of cancer. For studies here, an analysis of 150 cell lines derived from different cancers revealed no cases in which there was a homozygous loss of the BRCA2 gene. Because homozygous loss is apparently rare, investigations were made to study smaller lesions such as point mutations in BRCA2. Since compound mutant heterozygotes and mutant homozygotes are rare, tumor suppressor gene inactivation nearly always involves LOH. The remaining allele, if inactive, typically contains disruptive mutations. To identify these it is useful to preselect tumors or cell lines that exhibit LOH at the locus of interest.

Identification of tumors and cell lines that exhibit LOH

A group of 104 primary breast tumor samples and a set of 269 cell lines was tested for LOH in the BRCA2 region. For primary tumors, amplifications of three short tandem repeat markers (STRs) were compared quantitatively using fluorescence. Approximately 10 ng of genomic DNA was amplified by PCR with the following three sets of fluorescently tagged STRs:

(1) mM4247.4A.2F1 ACCATCAAACACATCATCC (SEQ ID NO: 119)

mM4247.4A.2R2 AGAAAGTAACTTGGAGGGAG (SEQ ID NO: 120)

(2) STR257-FC CTCCTGAAACTGTTCCCTTGG (SEQ ID NO: 121)

STR257-RD TAATGGTGCTGGGATATTTGG (SEQ ID NO: 122)

(3) mMB561A-3.1FA2 GAATGTCGAAGAGCTTGTC (SEQ ID NO: 123)

mMB561A-3.1RB AAACATACGCTTAGCCAGAC (SEQ ID NO: 124)

The PCR products were resolved using an ABI 377sequencer and quantified with Genescan software (ABI). For tumors, clear peak height differences between alleles amplified from normal and tumor samples were scored as having LOH. For cell lines, if one STR was heterozygous, the sample was scored as non-LOH. In only one case was a cell line or tumor miscalled based on later analysis of single base polymorphisms. The heterozygosity indices for the markers are: STR4247=0.89; STR257=0.72; STR561A=0.88 (S. Neuhausen, personal communication; B. Swedlund, unpublished data). Based on their combined heterozygosity indices, the chance that the markers are all homozygous in a particular individual (assuming linkage equilibrium) is only one in 250. Due to the presence of normal cells in the primary tumor sample, LOH seldom eliminates the signal entirely from the allele lost in the tumor. Rather, the relative intensities of the two alleles are altered. This can be seen clearly by comparing the allelic peak heights from normal tissue with peak heights from the tumor (FIGS. 5A–5D). Based on this analysis, 30 tumors (29%) were classified as having LOH at the BRCA2 locus (Table 5), a figure that is similar to previous estimates (Collins et al., 1995; Cleton-Jansen et al., 1995).

LOH was assessed in the set of cell lines in a different fashion. Since homozygosity of all three STRs was improbable, and since normal cells were not present, apparent homozygosity at all STRs was interpreted as LOH in the BRCA2 region. Using this criterion, 85/269 of the cell lines exhibited LOH (see Table 5). The frequencies varied according to the particular tumor cell type under consideration. For example, 4/6 ovarian cell lines and 31/62 lung cancer lines displayed LOH compared with 17/81 melanoma lines and 2/11 breast cancer lines.

Sequence Analysis of LOH Primary Breast Tumors and Cell Lines

The 30 primary breast cancers identified above which showed LOH in the BRCA2 region were screened by DNA sequence analysis for sequence variants. Greater than 95% of the coding sequence and splice junctions was examined. DNA sequencing was carried out either on the ABI 377 (Applied Biosystems Division, Perkin-Elmer) or manually. For the radioactive mutation screen, the amplified products were purified by Qiagen beads (Qiagen, Inc.). DNA sequence was generated using the Cyclist sequencing kit (Stratagene) and resolved on 6% polyacrylamide gels. In parallel, non-radioactive sequencing using fluorescent labeling dyes was performed using the TaqFS sequencing kit followed by electrophoresis on ABI 377sequencers. Samples were gridded into 96-well trays to facilitate PCR and sequencing. Dropouts of particular PCR and sequencing reactions were repeated until >95% coverage was obtained for every sample. Sequence information was analyzed with the Sequencher software (Gene Codes Corporation). All detected mutations were confirmed by sequencing a newly amplified PCR product to exclude the possibility that the sequence alteration was due to a PCR artifact.

TABLE 5

Type	# LOH/# Screened	Percentage LOH	# Sequenced
Astrocytoma	6/19	32%	6
Bladder	6/17	35%	4
Breast	2/11	18%	2
Colon	2/8	25%	2
Glioma	11/36	31%	5
Lung	31/62	50%	20
Lymphoma	0/4	0%	0
Melanoma	17/81	21%	9
Neuroblastoma	1/10	10%	1
Ovarian	4/6	67%	4
Pancreatic	1/3	33%	1
Prostate	0/2	0%	0
Renal	4/10	40%	4
Total	85/269	33% (avg. = 28%)	58
Primary Breast	30/104	29%	42

LOH analysis of cell lines and primary breast tumors. Percentage LOH was calculated two ways: as total and as a mean of percentages (avg.).

Of the 30samples, two specimens contained frameshift mutations, one a nonsense mutation, and two contained missense changes (although one of these tumors also contained a frameshift). The nonsense mutation would delete 156 codons at the C-terminus suggesting that the C-terminal end of BRCA2 is important for tumor suppressor activity. All sequence variants were also present in the corresponding normal DNA from these cancer patients. To exclude the unlikely possibility that preselection for LOH introduced a systematic bias against detecting mutations (e.g., dominant behavior of mutations, compound heterozygotes), 12samples shown to be heterozygous at BRCA2 were also screened. Three of these revealed missense changes that were also found in the normal samples. Thus, in a set of 42 breast carcinoma samples, 30 of which displayed LOH at the BRCA2 locus, no somatic mutations were identified. The frameshift and nonsense changes are likely to be predisposing mutations that influenced development of breast cancer in these patients. The missense variants are rare; they were each observed only once during analysis of 115 chromosomes. From these data it is not possible to distinguish between rare neutral polymorphisms and predisposing mutations.

Of the 85 cell lines which displayed LOH (see Table 5), 58 were also screened for sequence changes. Greater than 95% of the coding sequence of each sample was screened. Only a single frameshift mutation was identified by this DNA sequence analysis. This mutation (6174delT) was present in a pancreatic cancer line and it is identical to one found in the BT111 primary tumor sample and to a previously detected germline frameshift (Tavtigian et al., 1996). This suggests that this particular frameshift may be a relatively common germline BRCA2 mutation. In addition, a number of missense sequence variants were detected (Tables 6A and 6B).

Detection of a probable germline BRCA2 mutation in a pancreatic tumor cell line suggests that BRCA2 mutations may predispose to pancreatic cancer, a possibility that has not been explored thoroughly. This mutation also adds weight to the involvement of BRCA2 in sporadic pancreatic cancer, implied previously by the homozygous deletion observed in a pancreatic xenograft (Schutte et al., 1995). Because only three pancreatic cell lines were examined in our study, further investigation of BRCA2 mutations in pancreatic cancers is warranted.

TABLE 6A

Sample	Type	LOH	Change	Effect	Germline
4H5	Renal	yes	G451C	Ala→Pro	
4G1	Ovarian	yes	A1093C	Asn→His	
2F8	Lung	yes	G1291C	Val→Leu	
BT110	Primary breast	yes	1493delA	Frameshift	yes
4F8	Ovarian	yes	C2117T	Thr→Ile	
BT163	Primary breast	no	A2411C	Asp→Ala	yes
3D6	Bladder	no	G4813A	Gly→Arg	
BT333	Primary breast	no	T5868G	Asn→Lys	yes
2A2	Glioma	yes	C5972T	Thr→Met	
2I4	Lung	yes	C5972T	Thr→Met	
BT111	Primary breast	yes	6174delT	Frameshift	yes
4G3	Pancreatic	yes	6174delT	Frameshift	
1B7	Astrocytoma	yes	C6328T	Arg→Cys	
BT118	Primary breast	no	G7049T	Gly→Val	yes
BT115	Primary breast	yes	G7491C	Gln→His	yes
3D5	Melanoma	yes	A9537G	Ile→Met	
BT85	Primary breast	yes	A10204T	Lys→Stop	yes
1E4	Breast	yes	C10298G	Thr→Arg	
BT120	Primary breast	yes	A10462G	Ile→Val	yes

Germline mutations identified in BRCA2. Listed are the mutation positions based on the Genbank entry of BRCA2 (Schutte et al., 1995).

TABLE 6B

Position	Change	Effect	Frequency
5'UTR(203)	G/A	—	0.32 (0.26)
PM(1342)	C/A	His→Asn	0.32 (0.37)
PM(2457)	T/C	silent	0.04 (0.05)
PM(3199)	A/G	Asn→Asp	0.04 (0.08)
PM(3624)	A/G	silent	0.35
PM(3668)	A/G	Asn→Ser	0 (0.25)
PM(4035)	T/C	silent	0.24 (0.30)
PM(7470)	A/G	silent	0.26 (0.15)
1593	A→G	silent	<0.01
4296	G→A	silent	<0.01
5691	A→G	silent	<0.01
6051	A→G	silent	<0.01
6828	T→C	silent	<0.01
6921	T→C	silent	<0.01

Common polymorphisms and silent substitutions detected in BRCA2 by DNA sequencing. Since some rare silent variants may affect gene function (e.g., splicing (Richard and Beckmann, 1995)), these are not preceded by "PM". The frequencies of polymorphisms shown involve the second of the nucleotide pair. Frequencies reported in a previous study are shown in parentheses (Tavtigian et al., 1996). Numbering is as in Table 6A.

Industrial Utility

As previously described above, the present invention provides materials and methods for use in testing BRCA2 alleles of an individual and an interpretation of the normal or predisposing nature of the alleles. Individuals at higher than normal risk might modify their lifestyles appropriately. In the case of BRCA2, the most significant non-genetic risk factor is the protective effect of an early, full term pregnancy. Therefore, women at risk could consider early childbearing or a therapy designed to simulate the hormonal effects of an early full-term pregnancy. Women at high risk would also strive for early detection and would be more highly motivated to learn and practice breast self examination. Such women would also be highly motivated to have regular mammograms, perhaps starting at an earlier age than the general population. Ovarian screening could also be undertaken at greater frequency. Diagnostic methods based on sequence analysis of the BRCA2 locus could also be applied to tumor detection and classification. Sequence analysis could be used to diagnose precursor lesions. With the evolution of the method and the accumulation of information about BRCA2 and other causative loci, it could become possible to separate cancers into benign and malignant.

Women with breast cancers may follow different surgical procedures if they are predisposed, and therefore likely to have additional cancers, than if they are not predisposed. Other therapies may be developed, using either peptides or small molecules (rational drug design). Peptides could be the missing gene product itself or a portion of the missing gene product. Alternatively, the therapeutic agent could be another molecule that mimics the deleterious gene's function, either a peptide or a nonpeptidic molecule that seeks to counteract the deleterious effect of the inherited locus. The therapy could also be gene based, through introduction of a normal BRCA2 allele into individuals to make a protein which will counteract the effect of the deleterious allele. These gene therapies may take many forms and may be directed either toward preventing the tumor from forming, curing a cancer once it has occurred, or stopping a cancer from metastasizing.

It will be appreciated that the methods and compositions of the instant invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent to the artisan that other embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

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List of Patents and Patent Applications

U.S. Pat. No. 3,817,837
U.S. Pat. No. 3,850,752
U.S. Pat. No. 3,939,350
U.S. Pat. No. 3,996,345
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U.S. Pat. No. 4,277,437
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U.S. Pat. No. 4,376,110
U.S. Pat. No. 4,486,530
U.S. Pat. No. 4,683,195
U.S. Pat. No. 4,683,202
U.S. Pat. No. 4,816,567
U.S. Pat. No. 4,868,105
U.S. Pat. No. 5,252,479
EPO Publication No. 225,807
European Patent Application Publication No. 0332435
Geysen, H., PCT published application WO 84/03564, published 13 Sep. 1984
Hitzeman et al., EP 73,675A
PCT published application WO 93/07282

SEQUENCE LISTING

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( 1 ) GENERAL INFORMATION:

      ( i i i ) NUMBER OF SEQUENCES: 124

( 2 ) INFORMATION FOR SEQ ID NO:1:

      ( i ) SEQUENCE CHARACTERISTICS:
            ( A ) LENGTH: 11385 base pairs
            ( B ) TYPE: nucleic acid
            ( C ) STRANDEDNESS: single
            ( D ) TOPOLOGY: linear

      ( i i ) MOLECULE TYPE: cDNA

      ( i i i ) HYPOTHETICAL: NO

      ( i v ) ANTI-SENSE: NO

      ( v i ) ORIGINAL SOURCE:
            ( A ) ORGANISM: Homo sapiens

      ( i x ) FEATURE:
            ( A ) NAME/KEY: CDS
            ( B ) LOCATION: 229..10482

      ( x i ) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GGTGGCGCGA GCTTCTGAAA CTAGGCGGCA GAGGCGGAGC CGCTGTGGCA CTGCTGCGCC        60

TCTGCTGCGC CTCGGGTGTC TTTTGCGGCG GTGGGTCGCC GCCGGGAGAA GCGTGAGGGG       120

ACAGATTTGT GACCGGCGCG GTTTTTGTCA GCTTACTCCG GCCAAAAAAG AACTGCACCT       180

CTGGAGCGGA CTTATTTACC AAGCATTGGA GGAATATCGT AGGTAAAA ATG CCT ATT        237
                                                     Met Pro Ile
                                                       1

GGA TCC AAA GAG AGG CCA ACA TTT TTT GAA ATT TTT AAG ACA CGC TGC         285
Gly Ser Lys Glu Arg Pro Thr Phe Phe Glu Ile Phe Lys Thr Arg Cys
     5                  10                  15

AAC AAA GCA GAT TTA GGA CCA ATA AGT CTT AAT TGG TTT GAA GAA CTT         333
Asn Lys Ala Asp Leu Gly Pro Ile Ser Leu Asn Trp Phe Glu Glu Leu
 20                  25                  30                  35
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TCT TCA GAA GCT CCA CCC TAT AAT TCT GAA CCT GCA GAA GAA TCT GAA        381
Ser Ser Glu Ala Pro Pro Tyr Asn Ser Glu Pro Ala Glu Glu Ser Glu
                40                  45                  50

CAT AAA AAC AAC AAT TAC GAA CCA AAC CTA TTT AAA ACT CCA CAA AGG        429
His Lys Asn Asn Asn Tyr Glu Pro Asn Leu Phe Lys Thr Pro Gln Arg
            55                  60                  65

AAA CCA TCT TAT AAT CAG CTG GCT TCA ACT CCA ATA ATA TTC AAA GAG        477
Lys Pro Ser Tyr Asn Gln Leu Ala Ser Thr Pro Ile Ile Phe Lys Glu
        70                  75                  80

CAA GGG CTG ACT CTG CCG CTG TAC CAA TCT CCT GTA AAA GAA TTA GAT        525
Gln Gly Leu Thr Leu Pro Leu Tyr Gln Ser Pro Val Lys Glu Leu Asp
    85                  90                  95

AAA TTC AAA TTA GAC TTA GGA AGG AAT GTT CCC AAT AGT AGA CAT AAA        573
Lys Phe Lys Leu Asp Leu Gly Arg Asn Val Pro Asn Ser Arg His Lys
100                 105                 110                 115

AGT CTT CGC ACA GTG AAA ACT AAA ATG GAT CAA GCA GAT GAT GTT TCC        621
Ser Leu Arg Thr Val Lys Thr Lys Met Asp Gln Ala Asp Asp Val Ser
                120                 125                 130

TGT CCA CTT CTA AAT TCT TGT CTT AGT GAA AGT CCT GTT GTT CTA CAA        669
Cys Pro Leu Leu Asn Ser Cys Leu Ser Glu Ser Pro Val Val Leu Gln
            135                 140                 145

TGT ACA CAT GTA ACA CCA CAA AGA GAT AAG TCA GTG GTA TGT GGG AGT        717
Cys Thr His Val Thr Pro Gln Arg Asp Lys Ser Val Val Cys Gly Ser
        150                 155                 160

TTG TTT CAT ACA CCA AAG TTT GTG AAG GGT CGT CAG ACA CCA AAA CAT        765
Leu Phe His Thr Pro Lys Phe Val Lys Gly Arg Gln Thr Pro Lys His
    165                 170                 175

ATT TCT GAA AGT CTA GGA GCT GAG GTG GAT CCT GAT ATG TCT TGG TCA        813
Ile Ser Glu Ser Leu Gly Ala Glu Val Asp Pro Asp Met Ser Trp Ser
180                 185                 190                 195

AGT TCT TTA GCT ACA CCA CCC ACC CTT AGT TCT ACT GTG CTC ATA GTC        861
Ser Ser Leu Ala Thr Pro Pro Thr Leu Ser Ser Thr Val Leu Ile Val
                200                 205                 210

AGA AAT GAA GAA GCA TCT GAA ACT GTA TTT CCT CAT GAT ACT ACT GCT        909
Arg Asn Glu Glu Ala Ser Glu Thr Val Phe Pro His Asp Thr Thr Ala
            215                 220                 225

AAT GTG AAA AGC TAT TTT TCC AAT CAT GAT GAA AGT CTG AAG AAA AAT        957
Asn Val Lys Ser Tyr Phe Ser Asn His Asp Glu Ser Leu Lys Lys Asn
        230                 235                 240

GAT AGA TTT ATC GCT TCT GTG ACA GAC AGT GAA AAC ACA AAT CAA AGA       1005
Asp Arg Phe Ile Ala Ser Val Thr Asp Ser Glu Asn Thr Asn Gln Arg
    245                 250                 255

GAA GCT GCA AGT CAT GGA TTT GGA AAA ACA TCA GGG AAT TCA TTT AAA       1053
Glu Ala Ala Ser His Gly Phe Gly Lys Thr Ser Gly Asn Ser Phe Lys
260                 265                 270                 275

GTA AAT AGC TGC AAA GAC CAC ATT GGA AAG TCA ATG CCA AAT GTC CTA       1101
Val Asn Ser Cys Lys Asp His Ile Gly Lys Ser Met Pro Asn Val Leu
                280                 285                 290

GAA GAT GAA GTA TAT GAA ACA GTT GTA GAT ACC TCT GAA GAA GAT AGT       1149
Glu Asp Glu Val Tyr Glu Thr Val Val Asp Thr Ser Glu Glu Asp Ser
            295                 300                 305

TTT TCA TTA TGT TTT TCT AAA TGT AGA ACA AAA AAT CTA CAA AAA GTA       1197
Phe Ser Leu Cys Phe Ser Lys Cys Arg Thr Lys Asn Leu Gln Lys Val
        310                 315                 320

AGA ACT AGC AAG ACT AGG AAA AAA ATT TTC CAT GAA GCA AAC GCT GAT       1245
Arg Thr Ser Lys Thr Arg Lys Lys Ile Phe His Glu Ala Asn Ala Asp
    325                 330                 335

GAA TGT GAA AAA TCT AAA AAC CAA GTG AAA GAA AAA TAC TCA TTT GTA       1293
Glu Cys Glu Lys Ser Lys Asn Gln Val Lys Glu Lys Tyr Ser Phe Val
340                 345                 350                 355
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TCT GAA GTG GAA CCA AAT GAT ACT GAT CCA TTA GAT TCA AAT GTA GCA      1341
Ser Glu Val Glu Pro Asn Asp Thr Asp Pro Leu Asp Ser Asn Val Ala
                360                 365                 370

CAT CAG AAG CCC TTT GAG AGT GGA AGT GAC AAA ATC TCC AAG GAA GTT      1389
His Gln Lys Pro Phe Glu Ser Gly Ser Asp Lys Ile Ser Lys Glu Val
            375                 380                 385

GTA CCG TCT TTG GCC TGT GAA TGG TCT CAA CTA ACC CTT TCA GGT CTA      1437
Val Pro Ser Leu Ala Cys Glu Trp Ser Gln Leu Thr Leu Ser Gly Leu
        390                 395                 400

AAT GGA GCC CAG ATG GAG AAA ATA CCC CTA TTG CAT ATT TCT TCA TGT      1485
Asn Gly Ala Gln Met Glu Lys Ile Pro Leu Leu His Ile Ser Ser Cys
    405                 410                 415

GAC CAA AAT ATT TCA GAA AAA GAC CTA TTA GAC ACA GAG AAC AAA AGA      1533
Asp Gln Asn Ile Ser Glu Lys Asp Leu Leu Asp Thr Glu Asn Lys Arg
420                 425                 430                 435

AAG AAA GAT TTT CTT ACT TCA GAG AAT TCT TTG CCA CGT ATT TCT AGC      1581
Lys Lys Asp Phe Leu Thr Ser Glu Asn Ser Leu Pro Arg Ile Ser Ser
                440                 445                 450

CTA CCA AAA TCA GAG AAG CCA TTA AAT GAG GAA ACA GTG GTA AAT AAG      1629
Leu Pro Lys Ser Glu Lys Pro Leu Asn Glu Glu Thr Val Val Asn Lys
            455                 460                 465

AGA GAT GAA GAG CAG CAT CTT GAA TCT CAT ACA GAC TGC ATT CTT GCA      1677
Arg Asp Glu Glu Gln His Leu Glu Ser His Thr Asp Cys Ile Leu Ala
        470                 475                 480

GTA AAG CAG GCA ATA TCT GGA ACT TCT CCA GTG GCT TCT TCA TTT CAG      1725
Val Lys Gln Ala Ile Ser Gly Thr Ser Pro Val Ala Ser Ser Phe Gln
    485                 490                 495

GGT ATC AAA AAG TCT ATA TTC AGA ATA AGA GAA TCA CCT AAA GAG ACT      1773
Gly Ile Lys Lys Ser Ile Phe Arg Ile Arg Glu Ser Pro Lys Glu Thr
500                 505                 510                 515

TTC AAT GCA AGT TTT TCA GGT CAT ATG ACT GAT CCA AAC TTT AAA AAA      1821
Phe Asn Ala Ser Phe Ser Gly His Met Thr Asp Pro Asn Phe Lys Lys
                520                 525                 530

GAA ACT GAA GCC TCT GAA AGT GGA CTG GAA ATA CAT ACT GTT TGC TCA      1869
Glu Thr Glu Ala Ser Glu Ser Gly Leu Glu Ile His Thr Val Cys Ser
            535                 540                 545

CAG AAG GAG GAC TCC TTA TGT CCA AAT TTA ATT GAT AAT GGA AGC TGG      1917
Gln Lys Glu Asp Ser Leu Cys Pro Asn Leu Ile Asp Asn Gly Ser Trp
        550                 555                 560

CCA GCC ACC ACC ACA CAG AAT TCT GTA GCT TTG AAG AAT GCA GGT TTA      1965
Pro Ala Thr Thr Thr Gln Asn Ser Val Ala Leu Lys Asn Ala Gly Leu
    565                 570                 575

ATA TCC ACT TTG AAA AAG AAA ACA AAT AAG TTT ATT TAT GCT ATA CAT      2013
Ile Ser Thr Leu Lys Lys Lys Thr Asn Lys Phe Ile Tyr Ala Ile His
580                 585                 590                 595

GAT GAA ACA TCT TAT AAA GGA AAA AAA ATA CCG AAA GAC CAA AAA TCA      2061
Asp Glu Thr Ser Tyr Lys Gly Lys Lys Ile Pro Lys Asp Gln Lys Ser
                600                 605                 610

GAA CTA ATT AAC TGT TCA GCC CAG TTT GAA GCA AAT GCT TTT GAA GCA      2109
Glu Leu Ile Asn Cys Ser Ala Gln Phe Glu Ala Asn Ala Phe Glu Ala
            615                 620                 625

CCA CTT ACA TTT GCA AAT GCT GAT TCA GGT TTA TTG CAT TCT TCT GTG      2157
Pro Leu Thr Phe Ala Asn Ala Asp Ser Gly Leu Leu His Ser Ser Val
        630                 635                 640

AAA AGA AGC TGT TCA CAG AAT GAT TCT GAA GAA CCA ACT TTG TCC TTA      2205
Lys Arg Ser Cys Ser Gln Asn Asp Ser Glu Glu Pro Thr Leu Ser Leu
    645                 650                 655

ACT AGC TCT TTT GGG ACA ATT CTG AGG AAA TGT TCT AGA AAT GAA ACA      2253
Thr Ser Ser Phe Gly Thr Ile Leu Arg Lys Cys Ser Arg Asn Glu Thr
660                 665                 670                 675
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TGT TCT AAT AAT ACA GTA ATC TCT CAG GAT CTT GAT TAT AAA GAA GCA       2301
Cys Ser Asn Asn Thr Val Ile Ser Gln Asp Leu Asp Tyr Lys Glu Ala
                680                 685                 690

AAA TGT AAT AAG GAA AAA CTA CAG TTA TTT ATT ACC CCA GAA GCT GAT       2349
Lys Cys Asn Lys Glu Lys Leu Gln Leu Phe Ile Thr Pro Glu Ala Asp
            695                 700                 705

TCT CTG TCA TGC CTG CAG GAA GGA CAG TGT GAA AAT GAT CCA AAA AGC       2397
Ser Leu Ser Cys Leu Gln Glu Gly Gln Cys Glu Asn Asp Pro Lys Ser
        710                 715                 720

AAA AAA GTT TCA GAT ATA AAA GAA GAG GTC TTG GCT GCA GCA TGT CAC       2445
Lys Lys Val Ser Asp Ile Lys Glu Glu Val Leu Ala Ala Ala Cys His
    725                 730                 735

CCA GTA CAA CAT TCA AAA GTG GAA TAC AGT GAT ACT GAC TTT CAA TCC       2493
Pro Val Gln His Ser Lys Val Glu Tyr Ser Asp Thr Asp Phe Gln Ser
740                 745                 750                 755

CAG AAA AGT CTT TTA TAT GAT CAT GAA AAT GCC AGC ACT CTT ATT TTA       2541
Gln Lys Ser Leu Leu Tyr Asp His Glu Asn Ala Ser Thr Leu Ile Leu
                760                 765                 770

ACT CCT ACT TCC AAG GAT GTT CTG TCA AAC CTA GTC ATG ATT TCT AGA       2589
Thr Pro Thr Ser Lys Asp Val Leu Ser Asn Leu Val Met Ile Ser Arg
            775                 780                 785

GGC AAA GAA TCA TAC AAA ATG TCA GAC AAG CTC AAA GGT AAC AAT TAT       2637
Gly Lys Glu Ser Tyr Lys Met Ser Asp Lys Leu Lys Gly Asn Asn Tyr
        790                 795                 800

GAA TCT GAT GTT GAA TTA ACC AAA AAT ATT CCC ATG GAA AAG AAT CAA       2685
Glu Ser Asp Val Glu Leu Thr Lys Asn Ile Pro Met Glu Lys Asn Gln
    805                 810                 815

GAT GTA TGT GCT TTA AAT GAA AAT TAT AAA AAC GTT GAG CTG TTG CCA       2733
Asp Val Cys Ala Leu Asn Glu Asn Tyr Lys Asn Val Glu Leu Leu Pro
820                 825                 830                 835

CCT GAA AAA TAC ATG AGA GTA GCA TCA CCT TCA AGA AAG GTA CAA TTC       2781
Pro Glu Lys Tyr Met Arg Val Ala Ser Pro Ser Arg Lys Val Gln Phe
                840                 845                 850

AAC CAA AAC ACA AAT CTA AGA GTA ATC CAA AAA AAT CAA GAA GAA ACT       2829
Asn Gln Asn Thr Asn Leu Arg Val Ile Gln Lys Asn Gln Glu Glu Thr
            855                 860                 865

ACT TCA ATT TCA AAA ATA ACT GTC AAT CCA GAC TCT GAA GAA CTT TTC       2877
Thr Ser Ile Ser Lys Ile Thr Val Asn Pro Asp Ser Glu Glu Leu Phe
        870                 875                 880

TCA GAC AAT GAG AAT AAT TTT GTC TTC CAA GTA GCT AAT GAA AGG AAT       2925
Ser Asp Asn Glu Asn Asn Phe Val Phe Gln Val Ala Asn Glu Arg Asn
    885                 890                 895

AAT CTT GCT TTA GGA AAT ACT AAG GAA CTT CAT GAA ACA GAC TTG ACT       2973
Asn Leu Ala Leu Gly Asn Thr Lys Glu Leu His Glu Thr Asp Leu Thr
900                 905                 910                 915

TGT GTA AAC GAA CCC ATT TTC AAG AAC TCT ACC ATG GTT TTA TAT GGA       3021
Cys Val Asn Glu Pro Ile Phe Lys Asn Ser Thr Met Val Leu Tyr Gly
                920                 925                 930

GAC ACA GGT GAT AAA CAA GCA ACC CAA GTG TCA ATT AAA AAA GAT TTG       3069
Asp Thr Gly Asp Lys Gln Ala Thr Gln Val Ser Ile Lys Lys Asp Leu
            935                 940                 945

GTT TAT GTT CTT GCA GAG GAG AAC AAA AAT AGT GTA AAG CAG CAT ATA       3117
Val Tyr Val Leu Ala Glu Glu Asn Lys Asn Ser Val Lys Gln His Ile
        950                 955                 960

AAA ATG ACT CTA GGT CAA GAT TTA AAA TCG GAC ATC TCC TTG AAT ATA       3165
Lys Met Thr Leu Gly Gln Asp Leu Lys Ser Asp Ile Ser Leu Asn Ile
    965                 970                 975

GAT AAA ATA CCA GAA AAA AAT AAT GAT TAC ATG AAC AAA TGG GCA GGA       3213
Asp Lys Ile Pro Glu Lys Asn Asn Asp Tyr Met Asn Lys Trp Ala Gly
980                 985                 990                 995
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CTC TTA GGT CCA ATT TCA AAT CAC AGT TTT GGA GGT AGC TTC AGA ACA        3261
Leu Leu Gly Pro Ile Ser Asn His Ser Phe Gly Gly Ser Phe Arg Thr
                1000                1005                1010

GCT TCA AAT AAG GAA ATC AAG CTC TCT GAA CAT AAC ATT AAG AAG AGC        3309
Ala Ser Asn Lys Glu Ile Lys Leu Ser Glu His Asn Ile Lys Lys Ser
            1015                1020                1025

AAA ATG TTC TTC AAA GAT ATT GAA GAA CAA TAT CCT ACT AGT TTA GCT        3357
Lys Met Phe Phe Lys Asp Ile Glu Glu Gln Tyr Pro Thr Ser Leu Ala
        1030                1035                1040

TGT GTT GAA ATT GTA AAT ACC TTG GCA TTA GAT AAT CAA AAG AAA CTG        3405
Cys Val Glu Ile Val Asn Thr Leu Ala Leu Asp Asn Gln Lys Lys Leu
    1045                1050                1055

AGC AAG CCT CAG TCA ATT AAT ACT GTA TCT GCA CAT TTA CAG AGT AGT        3453
Ser Lys Pro Gln Ser Ile Asn Thr Val Ser Ala His Leu Gln Ser Ser
1060                1065                1070                1075

GTA GTT GTT TCT GAT TGT AAA AAT AGT CAT ATA ACC CCT CAG ATG TTA        3501
Val Val Val Ser Asp Cys Lys Asn Ser His Ile Thr Pro Gln Met Leu
                1080                1085                1090

TTT TCC AAG CAG GAT TTT AAT TCA AAC CAT AAT TTA ACA CCT AGC CAA        3549
Phe Ser Lys Gln Asp Phe Asn Ser Asn His Asn Leu Thr Pro Ser Gln
            1095                1100                1105

AAG GCA GAA ATT ACA GAA CTT TCT ACT ATA TTA GAA GAA TCA GGA AGT        3597
Lys Ala Glu Ile Thr Glu Leu Ser Thr Ile Leu Glu Glu Ser Gly Ser
        1110                1115                1120

CAG TTT GAA TTT ACT CAG TTT AGA AAA CCA AGC TAC ATA TTG CAG AAG        3645
Gln Phe Glu Phe Thr Gln Phe Arg Lys Pro Ser Tyr Ile Leu Gln Lys
    1125                1130                1135

AGT ACA TTT GAA GTG CCT GAA AAC CAG ATG ACT ATC TTA AAG ACC ACT        3693
Ser Thr Phe Glu Val Pro Glu Asn Gln Met Thr Ile Leu Lys Thr Thr
1140                1145                1150                1155

TCT GAG GAA TGC AGA GAT GCT GAT CTT CAT GTC ATA ATG AAT GCC CCA        3741
Ser Glu Glu Cys Arg Asp Ala Asp Leu His Val Ile Met Asn Ala Pro
                1160                1165                1170

TCG ATT GGT CAG GTA GAC AGC AGC AAG CAA TTT GAA GGT ACA GTT GAA        3789
Ser Ile Gly Gln Val Asp Ser Ser Lys Gln Phe Glu Gly Thr Val Glu
            1175                1180                1185

ATT AAA CGG AAG TTT GCT GGC CTG TTG AAA AAT GAC TGT AAC AAA AGT        3837
Ile Lys Arg Lys Phe Ala Gly Leu Leu Lys Asn Asp Cys Asn Lys Ser
        1190                1195                1200

GCT TCT GGT TAT TTA ACA GAT GAA AAT GAA GTG GGG TTT AGG GGC TTT        3885
Ala Ser Gly Tyr Leu Thr Asp Glu Asn Glu Val Gly Phe Arg Gly Phe
    1205                1210                1215

TAT TCT GCT CAT GGC ACA AAA CTG AAT GTT TCT ACT GAA GCT CTG CAA        3933
Tyr Ser Ala His Gly Thr Lys Leu Asn Val Ser Thr Glu Ala Leu Gln
1220                1225                1230                1235

AAA GCT GTG AAA CTG TTT AGT GAT ATT GAG AAT ATT AGT GAG GAA ACT        3981
Lys Ala Val Lys Leu Phe Ser Asp Ile Glu Asn Ile Ser Glu Glu Thr
                1240                1245                1250

TCT GCA GAG GTA CAT CCA ATA AGT TTA TCT TCA AGT AAA TGT CAT GAT        4029
Ser Ala Glu Val His Pro Ile Ser Leu Ser Ser Ser Lys Cys His Asp
            1255                1260                1265

TCT GTT GTT TCA ATG TTT AAG ATA GAA AAT CAT AAT GAT AAA ACT GTA        4077
Ser Val Val Ser Met Phe Lys Ile Glu Asn His Asn Asp Lys Thr Val
        1270                1275                1280

AGT GAA AAA AAT AAT AAA TGC CAA CTG ATA TTA CAA AAT AAT ATT GAA        4125
Ser Glu Lys Asn Asn Lys Cys Gln Leu Ile Leu Gln Asn Asn Ile Glu
    1285                1290                1295

ATG ACT ACT GGC ACT TTT GTT GAA GAA ATT ACT GAA AAT TAC AAG AGA        4173
Met Thr Thr Gly Thr Phe Val Glu Glu Ile Thr Glu Asn Tyr Lys Arg
1300                1305                1310                1315
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AAT ACT GAA AAT GAA GAT AAC AAA TAT ACT GCT GCC AGT AGA AAT TCT      4221
Asn Thr Glu Asn Glu Asp Asn Lys Tyr Thr Ala Ala Ser Arg Asn Ser
                1320                1325                1330

CAT AAC TTA GAA TTT GAT GGC AGT GAT TCA AGT AAA AAT GAT ACT GTT      4269
His Asn Leu Glu Phe Asp Gly Ser Asp Ser Ser Lys Asn Asp Thr Val
            1335                1340                1345

TGT ATT CAT AAA GAT GAA ACG GAC TTG CTA TTT ACT GAT CAG CAC AAC      4317
Cys Ile His Lys Asp Glu Thr Asp Leu Leu Phe Thr Asp Gln His Asn
        1350                1355                1360

ATA TGT CTT AAA TTA TCT GGC CAG TTT ATG AAG GAG GGA AAC ACT CAG      4365
Ile Cys Leu Lys Leu Ser Gly Gln Phe Met Lys Glu Gly Asn Thr Gln
    1365                1370                1375

ATT AAA GAA GAT TTG TCA GAT TTA ACT TTT TTG GAA GTT GCG AAA GCT      4413
Ile Lys Glu Asp Leu Ser Asp Leu Thr Phe Leu Glu Val Ala Lys Ala
1380                1385                1390                1395

CAA GAA GCA TGT CAT GGT AAT ACT TCA AAT AAA GAA CAG TTA ACT GCT      4461
Gln Glu Ala Cys His Gly Asn Thr Ser Asn Lys Glu Gln Leu Thr Ala
                1400                1405                1410

ACT AAA ACG GAG CAA AAT ATA AAA GAT TTT GAG ACT TCT GAT ACA TTT      4509
Thr Lys Thr Glu Gln Asn Ile Lys Asp Phe Glu Thr Ser Asp Thr Phe
            1415                1420                1425

TTT CAG ACT GCA AGT GGG AAA AAT ATT AGT GTC GCC AAA GAG TCA TTT      4557
Phe Gln Thr Ala Ser Gly Lys Asn Ile Ser Val Ala Lys Glu Ser Phe
        1430                1435                1440

AAT AAA ATT GTA AAT TTC TTT GAT CAG AAA CCA GAA GAA TTG CAT AAC      4605
Asn Lys Ile Val Asn Phe Phe Asp Gln Lys Pro Glu Glu Leu His Asn
    1445                1450                1455

TTT TCC TTA AAT TCT GAA TTA CAT TCT GAC ATA AGA AAG AAC AAA ATG      4653
Phe Ser Leu Asn Ser Glu Leu His Ser Asp Ile Arg Lys Asn Lys Met
1460                1465                1470                1475

GAC ATT CTA AGT TAT GAG GAA ACA GAC ATA GTT AAA CAC AAA ATA CTG      4701
Asp Ile Leu Ser Tyr Glu Glu Thr Asp Ile Val Lys His Lys Ile Leu
                1480                1485                1490

AAA GAA AGT GTC CCA GTT GGT ACT GGA AAT CAA CTA GTG ACC TTC CAG      4749
Lys Glu Ser Val Pro Val Gly Thr Gly Asn Gln Leu Val Thr Phe Gln
            1495                1500                1505

GGA CAA CCC GAA CGT GAT GAA AAG ATC AAA GAA CCT ACT CTG TTG GGT      4797
Gly Gln Pro Glu Arg Asp Glu Lys Ile Lys Glu Pro Thr Leu Leu Gly
        1510                1515                1520

TTT CAT ACA GCT AGC GGG AAA AAA GTT AAA ATT GCA AAG GAA TCT TTG      4845
Phe His Thr Ala Ser Gly Lys Lys Val Lys Ile Ala Lys Glu Ser Leu
    1525                1530                1535

GAC AAA GTG AAA AAC CTT TTT GAT GAA AAA GAG CAA GGT ACT AGT GAA      4893
Asp Lys Val Lys Asn Leu Phe Asp Glu Lys Glu Gln Gly Thr Ser Glu
1540                1545                1550                1555

ATC ACC AGT TTT AGC CAT CAA TGG GCA AAG ACC CTA AAG TAC AGA GAG      4941
Ile Thr Ser Phe Ser His Gln Trp Ala Lys Thr Leu Lys Tyr Arg Glu
                1560                1565                1570

GCC TGT AAA GAC CTT GAA TTA GCA TGT GAG ACC ATT GAG ATC ACA GCT      4989
Ala Cys Lys Asp Leu Glu Leu Ala Cys Glu Thr Ile Glu Ile Thr Ala
            1575                1580                1585

GCC CCA AAG TGT AAA GAA ATG CAG AAT TCT CTC AAT AAT GAT AAA AAC      5037
Ala Pro Lys Cys Lys Glu Met Gln Asn Ser Leu Asn Asn Asp Lys Asn
        1590                1595                1600

CTT GTT TCT ATT GAG ACT GTG GTG CCA CCT AAG CTC TTA AGT GAT AAT      5085
Leu Val Ser Ile Glu Thr Val Val Pro Pro Lys Leu Leu Ser Asp Asn
    1605                1610                1615

TTA TGT AGA CAA ACT GAA AAT CTC AAA ACA TCA AAA AGT ATC TTT TTG      5133
Leu Cys Arg Gln Thr Glu Asn Leu Lys Thr Ser Lys Ser Ile Phe Leu
1620                1625                1630                1635
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AAA GTT AAA GTA CAT GAA AAT GTA GAA AAA GAA ACA GCA AAA AGT CCT
Lys Val Lys Val His Glu Asn Val Glu Lys Glu Thr Ala Lys Ser Pro       5181
                1640                1645                1650

GCA ACT TGT TAC ACA AAT CAG TCC CCT TAT TCA GTC ATT GAA AAT TCA
Ala Thr Cys Tyr Thr Asn Gln Ser Pro Tyr Ser Val Ile Glu Asn Ser       5229
            1655                1660                1665

GCC TTA GCT TTT TAC ACA AGT TGT AGT AGA AAA ACT TCT GTG AGT CAG
Ala Leu Ala Phe Tyr Thr Ser Cys Ser Arg Lys Thr Ser Val Ser Gln       5277
        1670                1675                1680

ACT TCA TTA CTT GAA GCA AAA AAA TGG CTT AGA GAA GGA ATA TTT GAT
Thr Ser Leu Leu Glu Ala Lys Lys Trp Leu Arg Glu Gly Ile Phe Asp       5325
    1685                1690                1695

GGT CAA CCA GAA AGA ATA AAT ACT GCA GAT TAT GTA GGA AAT TAT TTG
Gly Gln Pro Glu Arg Ile Asn Thr Ala Asp Tyr Val Gly Asn Tyr Leu       5373
1700                1705                1710                1715

TAT GAA AAT AAT TCA AAC AGT ACT ATA GCT GAA AAT GAC AAA AAT CAT
Tyr Glu Asn Asn Ser Asn Ser Thr Ile Ala Glu Asn Asp Lys Asn His       5421
                1720                1725                1730

CTC TCC GAA AAA CAA GAT ACT TAT TTA AGT AAC AGT AGC ATG TCT AAC
Leu Ser Glu Lys Gln Asp Thr Tyr Leu Ser Asn Ser Ser Met Ser Asn       5469
            1735                1740                1745

AGC TAT TCC TAC CAT TCT GAT GAG GTA TAT AAT GAT TCA GGA TAT CTC
Ser Tyr Ser Tyr His Ser Asp Glu Val Tyr Asn Asp Ser Gly Tyr Leu       5517
        1750                1755                1760

TCA AAA AAT AAA CTT GAT TCT GGT ATT GAG CCA GTA TTG AAG AAT GTT
Ser Lys Asn Lys Leu Asp Ser Gly Ile Glu Pro Val Leu Lys Asn Val       5565
    1765                1770                1775

GAA GAT CAA AAA AAC ACT AGT TTT TCC AAA GTA ATA T[illegible] [illegible]AT GTA AAA
Glu Asp Gln Lys Asn Thr Ser Phe Ser Lys Val Ile Ser Asn Val Lys       5613
1780                1785                1790                1795

GAT GCA AAT GCA TAC CCA CAA ACT GTA AAT GAA GAT ATT TGC GTT GAG
Asp Ala Asn Ala Tyr Pro Gln Thr Val Asn Glu Asp Ile Cys Val Glu       5661
                1800                1805                1810

GAA CTT GTG ACT AGC TCT TCA CCC TGC AAA AAT AAA AAT GCA GCC ATT
Glu Leu Val Thr Ser Ser Ser Pro Cys Lys Asn Lys Asn Ala Ala Ile       5709
            1815                1820                1825

AAA TTG TCC ATA TCT AAT AGT AAT AAT TTT GAG GTA GGG CCA CCT GCA
Lys Leu Ser Ile Ser Asn Ser Asn Asn Phe Glu Val Gly Pro Pro Ala       5757
        1830                1835                1840

TTT AGG ATA GCC AGT GGT AAA ATC GTT TGT GTT TCA CAT GAA ACA ATT
Phe Arg Ile Ala Ser Gly Lys Ile Val Cys Val Ser His Glu Thr Ile       5805
    1845                1850                1855

AAA AAA GTG AAA GAC ATA TTT ACA GAC AGT TTC AGT AAA GTA ATT AAG
Lys Lys Val Lys Asp Ile Phe Thr Asp Ser Phe Ser Lys Val Ile Lys       5853
1860                1865                1870                1875

GAA AAC AAC GAG AAT AAA TCA AAA ATT TGC CAA ACG AAA ATT ATG GCA
Glu Asn Asn Glu Asn Lys Ser Lys Ile Cys Gln Thr Lys Ile Met Ala       5901
                1880                1885                1890

GGT TGT TAC GAG GCA TTG GAT GAT TCA GAG GAT ATT CTT CAT AAC TCT
Gly Cys Tyr Glu Ala Leu Asp Asp Ser Glu Asp Ile Leu His Asn Ser       5949
            1895                1900                1905

CTA GAT AAT GAT GAA TGT AGC ACG CAT TCA CAT AAG GTT TTT GCT GAC
Leu Asp Asn Asp Glu Cys Ser Thr His Ser His Lys Val Phe Ala Asp       5997
        1910                1915                1920

ATT CAG AGT GAA GAA ATT TTA CAA CAT AAC CAA AAT ATG TCT GGA TTG
Ile Gln Ser Glu Glu Ile Leu Gln His Asn Gln Asn Met Ser Gly Leu       6045
    1925                1930                1935

GAG AAA GTT TCT AAA ATA TCA CCT TGT GAT GTT AGT TTG GAA ACT TCA
Glu Lys Val Ser Lys Ile Ser Pro Cys Asp Val Ser Leu Glu Thr Ser       6093
1940                1945                1950                1955
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GAT ATA TGT AAA TGT AGT ATA GGG AAG CTT CAT AAG TCA GTC TCA TCT     6141
Asp Ile Cys Lys Cys Ser Ile Gly Lys Leu His Lys Ser Val Ser Ser
                1960                1965                1970

GCA AAT ACT TGT GGG ATT TTT AGC ACA GCA AGT GGA AAA TCT GTC CAG     6189
Ala Asn Thr Cys Gly Ile Phe Ser Thr Ala Ser Gly Lys Ser Val Gln
            1975                1980                1985

GTA TCA GAT GCT TCA TTA CAA AAC GCA AGA CAA GTG TTT TCT GAA ATA     6237
Val Ser Asp Ala Ser Leu Gln Asn Ala Arg Gln Val Phe Ser Glu Ile
        1990                1995                2000

GAA GAT AGT ACC AAG CAA GTC TTT TCC AAA GTA TTG TTT AAA AGT AAC     6285
Glu Asp Ser Thr Lys Gln Val Phe Ser Lys Val Leu Phe Lys Ser Asn
    2005                2010                2015

GAA CAT TCA GAC CAG CTC ACA AGA GAA GAA AAT ACT GCT ATA CGT ACT     6333
Glu His Ser Asp Gln Leu Thr Arg Glu Glu Asn Thr Ala Ile Arg Thr
2020                2025                2030                2035

CCA GAA CAT TTA ATA TCC CAA AAA GGC TTT TCA TAT AAT GTG GTA AAT     6381
Pro Glu His Leu Ile Ser Gln Lys Gly Phe Ser Tyr Asn Val Val Asn
                2040                2045                2050

TCA TCT GCT TTC TCT GGA TTT AGT ACA GCA AGT GGA AAG CAA GTT TCC     6429
Ser Ser Ala Phe Ser Gly Phe Ser Thr Ala Ser Gly Lys Gln Val Ser
            2055                2060                2065

ATT TTA GAA AGT TCC TTA CAC AAA GTT AAG GGA GTG TTA GAG GAA TTT     6477
Ile Leu Glu Ser Ser Leu His Lys Val Lys Gly Val Leu Glu Glu Phe
        2070                2075                2080

GAT TTA ATC AGA ACT GAG CAT AGT CTT CAC TAT TCA CCT ACG TCT AGA     6525
Asp Leu Ile Arg Thr Glu His Ser Leu His Tyr Ser Pro Thr Ser Arg
    2085                2090                2095

CAA AAT GTA TCA AAA ATA CTT CCT CGT GTT GAT AAG AGA AAC CCA GAG     6573
Gln Asn Val Ser Lys Ile Leu Pro Arg Val Asp Lys Arg Asn Pro Glu
2100                2105                2110                2115

CAC TGT GTA AAC TCA GAA ATG GAA AAA ACC TGC AGT AAA GAA TTT AAA     6621
His Cys Val Asn Ser Glu Met Glu Lys Thr Cys Ser Lys Glu Phe Lys
                2120                2125                2130

TTA TCA AAT AAC TTA AAT GTT GAA GGT GGT TCT TCA GAA AAT AAT CAC     6669
Leu Ser Asn Asn Leu Asn Val Glu Gly Gly Ser Ser Glu Asn Asn His
            2135                2140                2145

TCT ATT AAA GTT TCT CCA TAT CTC TCT CAA TTT CAA CAA GAC AAA CAA     6717
Ser Ile Lys Val Ser Pro Tyr Leu Ser Gln Phe Gln Gln Asp Lys Gln
        2150                2155                2160

CAG TTG GTA TTA GGA ACC AAA GTC TCA CTT GTT GAG AAC ATT CAT GTT     6765
Gln Leu Val Leu Gly Thr Lys Val Ser Leu Val Glu Asn Ile His Val
    2165                2170                2175

TTG GGA AAA GAA CAG GCT TCA CCT AAA AAC GTA AAA ATG GAA ATT GGT     6813
Leu Gly Lys Glu Gln Ala Ser Pro Lys Asn Val Lys Met Glu Ile Gly
2180                2185                2190                2195

AAA ACT GAA ACT TTT TCT GAT GTT CCT GTG AAA ACA AAT ATA GAA GTT     6861
Lys Thr Glu Thr Phe Ser Asp Val Pro Val Lys Thr Asn Ile Glu Val
                2200                2205                2210

TGT TCT ACT TAC TCC AAA GAT TCA GAA AAC TAC TTT GAA ACA GAA GCA     6909
Cys Ser Thr Tyr Ser Lys Asp Ser Glu Asn Tyr Phe Glu Thr Glu Ala
            2215                2220                2225

GTA GAA ATT GCT AAA GCT TTT ATG GAA GAT GAT GAA CTG ACA GAT TCT     6957
Val Glu Ile Ala Lys Ala Phe Met Glu Asp Asp Glu Leu Thr Asp Ser
        2230                2235                2240

AAA CTG CCA AGT CAT GCC ACA CAC TCT CCT TTT ACA TGT CCC GAA AAT     7005
Lys Leu Pro Ser His Ala Thr His Ser Pro Phe Thr Cys Pro Glu Asn
    2245                2250                2255

GAG GAA ATG GTT TTG TCA AAT TCA AGA ATT GGA AAA AGA AGA GGA GAG     7053
Glu Glu Met Val Leu Ser Asn Ser Arg Ile Gly Lys Arg Arg Gly Glu
2260                2265                2270                2275
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CCC CTT ATC TTA GTG GGA GAA CCC TCA ATC AAA AGA AAC TTA TTA AAT       7101
Pro Leu Ile Leu Val Gly Glu Pro Ser Ile Lys Arg Asn Leu Leu Asn
                2280                2285                2290

GAA TTT GAC AGG ATA ATA GAA AAT CAA GAA AAA TCC TTA AAG GCT TCA       7149
Glu Phe Asp Arg Ile Ile Glu Asn Gln Glu Lys Ser Leu Lys Ala Ser
            2295                2300                2305

AAA AGC ACT CCA GAT GGC ACA ATA AAA GAT CGA AGA TTG TTT ATG CAT       7197
Lys Ser Thr Pro Asp Gly Thr Ile Lys Asp Arg Arg Leu Phe Met His
        2310                2315                2320

CAT GTT TCT TTA GAG CCG ATT ACC TGT GTA CCC TTT CGC ACA ACT AAG       7245
His Val Ser Leu Glu Pro Ile Thr Cys Val Pro Phe Arg Thr Thr Lys
    2325                2330                2335

GAA CGT CAA GAG ATA CAG AAT CCA AAT TTT ACC GCA CCT GGT CAA GAA       7293
Glu Arg Gln Glu Ile Gln Asn Pro Asn Phe Thr Ala Pro Gly Gln Glu
2340                2345                2350                2355

TTT CTG TCT AAA TCT CAT TTG TAT GAA CAT CTG ACT TTG GAA AAA TCT       7341
Phe Leu Ser Lys Ser His Leu Tyr Glu His Leu Thr Leu Glu Lys Ser
                2360                2365                2370

TCA AGC AAT TTA GCA GTT TCA GGA CAT CCa TTT TAT CAA GTT TCT GCT       7389
Ser Ser Asn Leu Ala Val Ser Gly His Pro Phe Tyr Gln Val Ser Ala
            2375                2380                2385

ACA AGA AAT GAA AAA ATG AGA CAC TTG ATT ACT ACA GGC AGA CCA ACC       7437
Thr Arg Asn Glu Lys Met Arg His Leu Ile Thr Thr Gly Arg Pro Thr
        2390                2395                2400

AAA GTC TTT GTT CCA CCT TTT AAA ACT AAA TCA CAT TTT CAC AGA GTT       7485
Lys Val Phe Val Pro Pro Phe Lys Thr Lys Ser His Phe His Arg Val
    2405                2410                2415

GAA CAG TGT GTT AGG AAT ATT AAC TTG GAG GAA AAC AGA CAA AAG CAA       7533
Glu Gln Cys Val Arg Asn Ile Asn Leu Glu Glu Asn Arg Gln Lys Gln
2420                2425                2430                2435

AAC ATT GAT GGA CAT GGC TCT GAT GAT AGT AAA AAT AAG ATT AAT GAC       7581
Asn Ile Asp Gly His Gly Ser Asp Asp Ser Lys Asn Lys Ile Asn Asp
                2440                2445                2450

AAT GAG ATT CAT CAG TTT AAC AAa AAC AAC TCC AAT CAA GCA GCA GCT       7629
Asn Glu Ile His Gln Phe Asn Lys Asn Asn Ser Asn Gln Ala Ala Ala
            2455                2460                2465

GTA ACT TTC ACA AAG TGT GAA GAA GAA CCT TTA GAT TTA ATT ACA AGT       7677
Val Thr Phe Thr Lys Cys Glu Glu Glu Pro Leu Asp Leu Ile Thr Ser
        2470                2475                2480

CTT CAG AAT GCC AGA GAT ATA CAG GAT ATG CGA ATT AAG AAG AAA CAA       7725
Leu Gln Asn Ala Arg Asp Ile Gln Asp Met Arg Ile Lys Lys Lys Gln
    2485                2490                2495

AGG CAA CGC GTC TTT CCA CAG CCA GGC AGT CTG TAT CTT GCA AAA ACA       7773
Arg Gln Arg Val Phe Pro Gln Pro Gly Ser Leu Tyr Leu Ala Lys Thr
2500                2505                2510                2515

TCC ACT CTG CCT CGA ATC TCT CTG AAA GCA GCA GTA GGA GGC CAA GTT       7821
Ser Thr Leu Pro Arg Ile Ser Leu Lys Ala Ala Val Gly Gly Gln Val
                2520                2525                2530

CCC TCT GCG TGT TCT CAT AAA CAG CTG TAT ACG TAT GGC GTT TCT AAA       7869
Pro Ser Ala Cys Ser His Lys Gln Leu Tyr Thr Tyr Gly Val Ser Lys
            2535                2540                2545

CAT TGC ATA AAA ATT AAC AGC AAA AAT GCA GAG TCT TTT CAG TTT CAC       7917
His Cys Ile Lys Ile Asn Ser Lys Asn Ala Glu Ser Phe Gln Phe His
        2550                2555                2560

ACT GAA GAT TAT TTT GGT AAG GAA AGT TTA TGG ACT GGA AAA GGA ATA       7965
Thr Glu Asp Tyr Phe Gly Lys Glu Ser Leu Trp Thr Gly Lys Gly Ile
    2565                2570                2575

CAG TTG GCT GAT GGT GGA TGG CTC ATA CCC TCC AAT GAT GGA AAG GCT       8013
Gln Leu Ala Asp Gly Gly Trp Leu Ile Pro Ser Asn Asp Gly Lys Ala
2580                2585                2590                2595
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GGA AAA GAA GAA TTT TAT AGG GCT CTG TGT GAC ACT CCA GGT GTG GAT       8061
Gly Lys Glu Glu Phe Tyr Arg Ala Leu Cys Asp Thr Pro Gly Val Asp
                2600                2605                2610

CCA AAG CTT ATT TCT AGA ATT TGG GTT TAT AAT CAC TAT AGA TGG ATC       8109
Pro Lys Leu Ile Ser Arg Ile Trp Val Tyr Asn His Tyr Arg Trp Ile
            2615                2620                2625

ATA TGG AAA CTG GCA GCT ATG GAA TGT GCC TTT CCT AAG GAA TTT GCT       8157
Ile Trp Lys Leu Ala Ala Met Glu Cys Ala Phe Pro Lys Glu Phe Ala
        2630                2635                2640

AAT AGA TGC CTA AGC CCA GAA AGG GTG CTT CTT CAA CTA AAA TAC AGA       8205
Asn Arg Cys Leu Ser Pro Glu Arg Val Leu Leu Gln Leu Lys Tyr Arg
    2645                2650                2655

TAT GAT ACG GAA ATT GAT AGA AGC AGA AGA TCG GCT ATA AAA AAG ATA       8253
Tyr Asp Thr Glu Ile Asp Arg Ser Arg Arg Ser Ala Ile Lys Lys Ile
2660                2665                2670                2675

ATG GAA AGG GAT GAC ACA GCT GCA AAA ACA CTT GTT CTC TGT GTT TCT       8301
Met Glu Arg Asp Asp Thr Ala Ala Lys Thr Leu Val Leu Cys Val Ser
                2680                2685                2690

GAC ATA ATT TCA TTG AGC GCA AAT ATA TCT GAA ACT TCT AGC AAT AAA       8349
Asp Ile Ile Ser Leu Ser Ala Asn Ile Ser Glu Thr Ser Ser Asn Lys
            2695                2700                2705

ACT AGT AGT GCA GAT ACC CAA AAA GTG GCC ATT ATT GAA CTT ACA GAT       8397
Thr Ser Ser Ala Asp Thr Gln Lys Val Ala Ile Ile Glu Leu Thr Asp
        2710                2715                2720

GGG TGG TAT GCT GTT AAG GCC CAG TTA GAT CCT CCC CTC TTA GCT GTC       8445
Gly Trp Tyr Ala Val Lys Ala Gln Leu Asp Pro Pro Leu Leu Ala Val
    2725                2730                2735

TTA AAG AAT GGC AGA CTG ACA GTT GGT CAG AAG ATT ATT CTT CAT GGA       8493
Leu Lys Asn Gly Arg Leu Thr Val Gly Gln Lys Ile Ile Leu His Gly
2740                2745                2750                2755

GCA GAA CTG GTG GGC TCT CCT GAT GCC TGT ACA CCT CTT GAA GCC CCA       8541
Ala Glu Leu Val Gly Ser Pro Asp Ala Cys Thr Pro Leu Glu Ala Pro
                2760                2765                2770

GAA TCT CTT ATG TTA AAG ATT TCT GCT AAC AGT ACT CGG CCT GCT CGC       8589
Glu Ser Leu Met Leu Lys Ile Ser Ala Asn Ser Thr Arg Pro Ala Arg
            2775                2780                2785

TGG TAT ACC AAA CTT GGA TTC TTT CCT GAC CCT AGA CCT TTT CCT CTG       8637
Trp Tyr Thr Lys Leu Gly Phe Phe Pro Asp Pro Arg Pro Phe Pro Leu
        2790                2795                2800

CCC TTA TCA TCG CTT TTC AGT GAT GGA GGA AAT GTT GGT TGT GTT GAT       8685
Pro Leu Ser Ser Leu Phe Ser Asp Gly Gly Asn Val Gly Cys Val Asp
    2805                2810                2815

GTA ATT ATT CAA AGA GCA TAC CCT ATA CAG TGG ATG GAG AAG ACA TCA       8733
Val Ile Ile Gln Arg Ala Tyr Pro Ile Gln Trp Met Glu Lys Thr Ser
2820                2825                2830                2835

TCT GGA TTA TAC ATA TTT CGC AAT GAA AGA GAG GAA GAA AAG GAA GCA       8781
Ser Gly Leu Tyr Ile Phe Arg Asn Glu Arg Glu Glu Glu Lys Glu Ala
                2840                2845                2850

GCA AAA TAT GTG GAG GCC CAA CAA AAG AGA CTA GAA GCC TTA TTC ACT       8829
Ala Lys Tyr Val Glu Ala Gln Gln Lys Arg Leu Glu Ala Leu Phe Thr
            2855                2860                2865

AAA ATT CAG GAG GAA TTT GAA GAA CAT GAA GAA AAC ACA ACA AAA CCA       8877
Lys Ile Gln Glu Glu Phe Glu Glu His Glu Glu Asn Thr Thr Lys Pro
        2870                2875                2880

TAT TTA CCA TCA CGT GCA CTA ACA AGA CAG CAA GTT C[illegible] [illegible]CT TTG CAA       8925
Tyr Leu Pro Ser Arg Ala Leu Thr Arg Gln Gln Val Arg Ala Leu Gln
    2885                2890                2895

GAT GGT GCA GAG CTT TAT GAA GCA GTG AAG AAT GCA GCA GAC CCA GCT       8973
Asp Gly Ala Glu Leu Tyr Glu Ala Val Lys Asn Ala Ala Asp Pro Ala
2900                2905                2910                2915
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TAC CTT GAG GGT TAT TTC AGT GAA GAG CAG TTA AGA GCC TTG AAT AAT       9021
Tyr Leu Glu Gly Tyr Phe Ser Glu Glu Gln Leu Arg Ala Leu Asn Asn
                2920                2925                2930

CAC AGG CAA ATG TTG AAT GAT AAG AAA CAA GCT CAG ATC CAG TTG GAA       9069
His Arg Gln Met Leu Asn Asp Lys Lys Gln Ala Gln Ile Gln Leu Glu
            2935                2940                2945

ATT AGG AAG GCC ATG GAA TCT GCT GAA CAA AAG GAA CAA GGT TTA TCA       9117
Ile Arg Lys Ala Met Glu Ser Ala Glu Gln Lys Glu Gln Gly Leu Ser
        2950                2955                2960

AGG GAT GTC ACA ACC GTG TGG AAG TTG CGT ATT GTA AGC TAT TCA AAA       9165
Arg Asp Val Thr Thr Val Trp Lys Leu Arg Ile Val Ser Tyr Ser Lys
    2965                2970                2975

AAA GAA AAA GAT TCA GTT ATA CTG AGT ATT TGG CGT CCA TCA TCA GAT       9213
Lys Glu Lys Asp Ser Val Ile Leu Ser Ile Trp Arg Pro Ser Ser Asp
2980                2985                2990                2995

TTA TAT TCT CTG TTA ACA GAA GGA AAG AGA TAC AGA ATT TAT CAT CTT       9261
Leu Tyr Ser Leu Leu Thr Glu Gly Lys Arg Tyr Arg Ile Tyr His Leu
                3000                3005                3010

GCA ACT TCA AAA TCT AAA AGT AAA TCT GAA AGA GCT AAC ATA CAG TTA       9309
Ala Thr Ser Lys Ser Lys Ser Lys Ser Glu Arg Ala Asn Ile Gln Leu
            3015                3020                3025

GCA GCG ACA AAA AAA ACT CAG TAT CAA CAA CTA CCG GTT TCA GAT GAA       9357
Ala Ala Thr Lys Lys Thr Gln Tyr Gln Gln Leu Pro Val Ser Asp Glu
        3030                3035                3040

ATT TTA TTT CAG ATT TAC CAG CCA CGG GAG CCC CTT CAC TTC AGC AAA       9405
Ile Leu Phe Gln Ile Tyr Gln Pro Arg Glu Pro Leu His Phe Ser Lys
    3045                3050                3055

TTT TTA GAT CCA GAC TTT CAG CCA TCT TGT TCT GAG GTG GAC CTA ATA       9453
Phe Leu Asp Pro Asp Phe Gln Pro Ser Cys Ser Glu Val Asp Leu Ile
3060                3065                3070                3075

GGA TTT GTC GTT TCT GTT GTG AAA AAA ACA GGA CTT GCC CCT TTC GTC       9501
Gly Phe Val Val Ser Val Val Lys Lys Thr Gly Leu Ala Pro Phe Val
                3080                3085                3090

TAT TTG TCA GAC GAA TGT TAC AAT TTA CTG GCA ATA AAG TTT TGG ATA       9549
Tyr Leu Ser Asp Glu Cys Tyr Asn Leu Leu Ala Ile Lys Phe Trp Ile
            3095                3100                3105

GAC CTT AAT GAG GAC ATT ATT AAG CCT CAT ATG TTA ATT GCT GCA AGC       9597
Asp Leu Asn Glu Asp Ile Ile Lys Pro His Met Leu Ile Ala Ala Ser
        3110                3115                3120

AAC CTC CAG TGG CGA CCA GAA TCC AAA TCA GGC CTT CTT ACT TTA TTT       9645
Asn Leu Gln Trp Arg Pro Glu Ser Lys Ser Gly Leu Leu Thr Leu Phe
    3125                3130                3135

GCT GGA GAT TTT TCT GTG TTT TCT GCT AGT CCA AAA GAG GGC CAC TTT       9693
Ala Gly Asp Phe Ser Val Phe Ser Ala Ser Pro Lys Glu Gly His Phe
3140                3145                3150                3155

CAA GAG ACA TTC AAC AAA ATG AAA AAT ACT GTT GAG AAT ATT GAC ATA       9741
Gln Glu Thr Phe Asn Lys Met Lys Asn Thr Val Glu Asn Ile Asp Ile
                3160                3165                3170

CTT TGC AAT GAA GCA GAA AAC AAG CTT ATG CAT ATA CTG CAT GCA AAT       9789
Leu Cys Asn Glu Ala Glu Asn Lys Leu Met His Ile Leu His Ala Asn
            3175                3180                3185

GAT CCC AAG TGG TCC ACC CCA ACT AAA GAC TGT ACT TCA GGG CCG TAC       9837
Asp Pro Lys Trp Ser Thr Pro Thr Lys Asp Cys Thr Ser Gly Pro Tyr
        3190                3195                3200

ACT GCT CAA ATC ATT CCT GGT ACA GGA AAC AAG CTT CTG ATG TCT TCT       9885
Thr Ala Gln Ile Ile Pro Gly Thr Gly Asn Lys Leu Leu Met Ser Ser
    3205                3210                3215

CCT AAT TGT GAG ATA TAT TAT CAA AGT CCT TTA TCA CTT TGT ATG GCC       9933
Pro Asn Cys Glu Ile Tyr Tyr Gln Ser Pro Leu Ser Leu Cys Met Ala
3220                3225                3230                3235
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AAA AGG AAG TCT GTT TCC ACA CCT GTC TCA GCC CAG ATG ACT TCA AAG        9981
Lys Arg Lys Ser Val Ser Thr Pro Val Ser Ala Gln Met Thr Ser Lys
                3240                3245                3250

TCT TGT AAA GGG GAG AAA GAG ATT GAT GAC CAA AAG AAC TGC AAA AAG       10029
Ser Cys Lys Gly Glu Lys Glu Ile Asp Asp Gln Lys Asn Cys Lys Lys
            3255                3260                3265

AGA AGA GCC TTG GAT TTC TTG AGT AGA CTG CCT TTA CCT CCA CCT GTT       10077
Arg Arg Ala Leu Asp Phe Leu Ser Arg Leu Pro Leu Pro Pro Pro Val
        3270                3275                3280

AGT CCC ATT TGT ACA TTT GTT TCT CCG GCT GCA CAG AAG GCA TTT CAG       10125
Ser Pro Ile Cys Thr Phe Val Ser Pro Ala Ala Gln Lys Ala Phe Gln
    3285                3290                3295

CCA CCA AGG AGT TGT GGC ACC AAA TAC GAA ACA CCC ATA AAG AAA AAA       10173
Pro Pro Arg Ser Cys Gly Thr Lys Tyr Glu Thr Pro Ile Lys Lys Lys
3300                3305                3310                3315

GAA CTG AAT TCT CCT CAG ATG ACT CCA TTT AAA AAA TTC AAT GAA ATT       10221
Glu Leu Asn Ser Pro Gln Met Thr Pro Phe Lys Lys Phe Asn Glu Ile
                3320                3325                3330

TCT CTT TTG GAA AGT AAT TCA ATA GCT GAC GAA GAA CTT GCA TTG ATA       10269
Ser Leu Leu Glu Ser Asn Ser Ile Ala Asp Glu Glu Leu Ala Leu Ile
            3335                3340                3345

AAT ACC CAA GCT CTT TTG TCT GGT TCA ACA GGA GAA AAA CAA TTT ATA       10317
Asn Thr Gln Ala Leu Leu Ser Gly Ser Thr Gly Glu Lys Gln Phe Ile
        3350                3355                3360

TCT GTC AGT GAA TCC ACT AGG ACT GCT CCC ACC AGT TCA GAA GAT TAT       10365
Ser Val Ser Glu Ser Thr Arg Thr Ala Pro Thr Ser Ser Glu Asp Tyr
    3365                3370                3375

CTC AGA CTG AAA CGA CGT TGT ACT ACA TCT CTG ATC AAA GAA CAG GAG       10413
Leu Arg Leu Lys Arg Arg Cys Thr Thr Ser Leu Ile Lys Glu Gln Glu
3380                3385                3390                3395

AGT TCC CAG GCC AGT ACG GAA GAA TGT GAG AAA AAT AAG CAG GAC ACA       10461
Ser Ser Gln Ala Ser Thr Glu Glu Cys Glu Lys Asn Lys Gln Asp Thr
                3400                3405                3410

ATT ACA ACT AAA AAA TAT ATC TAAGCATTTG CAAAGGCGAC AATAAATTAT          10512
Ile Thr Thr Lys Lys Tyr Ile
            3415

TGACGCTTAA CCTTTCCAGT TTATAAGACT GGAATATAAT TTCAAACCAC ACATTAGTAC   10572

TTATGTTGCA CAATGAGAAA AGAAATTAGT TTCAAATTTA CCTCAGCGTT TGTGTATCGG   10632

GCAAAAATCG TTTTGCCCGA TTCCGTATTG GTATACTTTT GCTTCAGTTG CATATCTTAA   10692

AACTAAATGT AATTTATTAA CTAATCAAGA AAAACATCTT TGGCTGAGCT CGGTGGCTCA   10752

TGCCTGTAAT CCCAACACTT TGAGAAGCTG AGGTGGCAGG AGTGCTTGAG GCCAGGAGTT   10812

CAAGACCAGC CTGGGCAACA TAGGGAGACC CCCATCTTTA CGAAGAAAAA AAAAAAGGGG   10872

AAAAGAAAAT CTTTTAAATC TTTGGATTTG ATCACTACAA GTATTATTTT ACAAGTGAAA   10932

TAAACATACC ATTTTCTTTT AGATTGTGTC ATTAAATGGA ATGAGGTCTC TTAGTACAGT   10992

TATTTTCATG CAGATAATTC CTTTTAGTTT AGCTACTATT TTAGGGGATT TTTTTTAGAG   11052

GTAACTCACT ATGAAATAGT TCTCCTTAAT GCAAATATGT TGGTTCTGCT ATAGTTCCAT   11112

CCTGTTCAAA AGTCAGGATG AATATGAAGA GTGGTGTTTC CTTTTGAGCA ATTCTTCATC   11172

CTTAAGTCAG CATGATTATA AGAAAAATAG AACCCTCAGT GTAACTCTAA TTCCTTTTTA   11232

CTATTCCAGT GTGATCTCTG AAATTAAATT ACTTCAACTA AAAATTCAAA TACTTTAAAT   11292

CAGAAGATTT CATAGTTAAT TTATTTTTTT TTTCAACAAA ATGGTCATCC AAACTCAAAC   11352

TTGAGAAAAT ATCTTGCTTT CAAATTGACA CTA                                11385
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(2) INFORMATION FOR SEQ ID NO:2:

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(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3418 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: protein

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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Met Pro Ile Gly Ser Lys Glu Arg Pro Thr Phe Phe Glu Ile Phe Lys
1               5                   10                  15

Thr Arg Cys Asn Lys Ala Asp Leu Gly Pro Ile Ser Leu Asn Trp Phe
            20                  25                  30

Glu Glu Leu Ser Ser Glu Ala Pro Pro Tyr Asn Ser Glu Pro Ala Glu
        35                  40                  45

Glu Ser Glu His Lys Asn Asn Asn Tyr Glu Pro Asn Leu Phe Lys Thr
    50                  55                  60

Pro Gln Arg Lys Pro Ser Tyr Asn Gln Leu Ala Ser Thr Pro Ile Ile
65                  70                  75                  80

Phe Lys Glu Gln Gly Leu Thr Leu Pro Leu Tyr Gln Ser Pro Val Lys
                85                  90                  95

Glu Leu Asp Lys Phe Lys Leu Asp Leu Gly Arg Asn Val Pro Asn Ser
            100                 105                 110

Arg His Lys Ser Leu Arg Thr Val Lys Thr Lys Met Asp Gln Ala Asp
        115                 120                 125

Asp Val Ser Cys Pro Leu Leu Asn Ser Cys Leu Ser Glu Ser Pro Val
    130                 135                 140

Val Leu Gln Cys Thr His Val Thr Pro Glu Arg Asp Lys Ser Val Val
145                 150                 155                 160

Cys Gly Ser Leu Phe His Thr Pro Lys Phe Val Lys Gly Arg Gln Thr
                165                 170                 175

Pro Lys His Ile Ser Glu Ser Leu Gly Ala Glu Val Asp Pro Asp Met
            180                 185                 190

Ser Trp Ser Ser Ser Leu Ala Thr Pro Pro Thr Leu Ser Ser Thr Val
        195                 200                 205

Leu Ile Val Arg Asn Glu Gln Ala Ser Gln Thr Val Phe Pro His Asp
    210                 215                 220

Thr Thr Ala Asn Val Lys Ser Tyr Phe Ser Asn His Asp Glu Ser Leu
225                 230                 235                 240

Lys Lys Asn Asp Arg Phe Ile Ala Ser Val Thr Asp Ser Glu Asn Thr
                245                 250                 255

Asn Gln Arg Glu Ala Ala Ser His Gly Phe Gly Lys Thr Ser Gly Asn
            260                 265                 270

Ser Phe Lys Val Asn Ser Cys Lys Asp His Ile Gly Lys Ser Met Pro
        275                 280                 285

Asn Val Leu Glu Asp Glu Val Tyr Glu Thr Val Val Asp Thr Ser Glu
    290                 295                 300

Glu Asp Ser Phe Ser Leu Cys Phe Ser Lys Cys Arg Thr Lys Asn Leu
305                 310                 315                 320

Gln Lys Val Arg Thr Ser Lys Thr Arg Lys Lys Ile Phe His Glu Ala
                325                 330                 335

Asn Ala Asp Glu Cys Glu Lys Ser Lys Asn Glu Val Lys Glu Lys Tyr
            340                 345                 350

Ser Phe Val Ser Glu Val Glu Pro Asn Asp Thr Asp Pro Leu Asp Ser
        355                 360                 365
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Asn Val Ala His Gln Lys Pro Phe Glu Ser Gly Ser Asp Lys Ile Ser
    370                 375                 380

Lys Glu Val Val Pro Ser Leu Ala Cys Glu Trp Ser Gln Leu Thr Leu
385                 390                 395                 400

Ser Gly Leu Asn Gly Ala Gln Met Glu Lys Ile Pro Leu Leu His Ile
                405                 410                 415

Ser Ser Cys Asp Gln Asn Ile Ser Glu Lys Asp Leu Leu Asp Thr Glu
            420                 425                 430

Asn Lys Arg Lys Lys Asp Phe Leu Thr Ser Gln Asn Ser Leu Pro Arg
        435                 440                 445

Ile Ser Ser Leu Pro Lys Ser Glu Lys Pro Leu Asn Glu Glu Thr Val
    450                 455                 460

Val Asn Lys Arg Asp Glu Glu Gln His Leu Glu Ser His Thr Asp Cys
465                 470                 475                 480

Ile Leu Ala Val Lys Gln Ala Ile Ser Gly Thr Ser Pro Val Ala Ser
                485                 490                 495

Ser Phe Gln Gly Ile Lys Lys Ser Ile Phe Arg Ile Arg Glu Ser Pro
            500                 505                 510

Lys Glu Thr Phe Asn Ala Ser Phe Ser Gly His Met Thr Asp Pro Asn
        515                 520                 525

Phe Lys Lys Glu Thr Glu Ala Ser Glu Ser Gly Leu Gln Ile His Thr
    530                 535                 540

Val Cys Ser Glu Lys Glu Asp Ser Leu Cys Pro Asn Leu Ile Asp Asn
545                 550                 555                 560

Gly Ser Trp Pro Ala Thr Thr Thr Gln Asn Ser Val Ala Leu Lys Asn
                565                 570                 575

Ala Gly Leu Ile Ser Thr Leu Lys Lys Lys Thr Asn Lys Phe Ile Tyr
            580                 585                 590

Ala Ile His Asp Glu Thr Phe Tyr Lys Gly Lys Lys Ile Pro Lys Asp
        595                 600                 605

Glu Lys Ser Glu Leu Ile Asn Cys Ser Ala Gln Phe Glu Ala Asn Ala
    610                 615                 620

Phe Glu Ala Pro Leu Thr Phe Ala Asn Ala Asp Ser Gly Leu Leu His
625                 630                 635                 640

Ser Ser Val Lys Arg Ser Cys Ser Gln Asn Asp Ser Glu Glu Pro Thr
                645                 650                 655

Leu Ser Leu Thr Ser Ser Phe Gly Thr Ile Leu Arg Lys Cys Ser Arg
            660                 665                 670

Asn Glu Thr Cys Ser Asn Asn Thr Val Ile Ser Gln Asp Leu Asp Tyr
        675                 680                 685

Lys Glu Ala Lys Cys Asn Lys Glu Lys Leu Gln Leu Phe Ile Thr Pro
    690                 695                 700

Glu Ala Asp Ser Leu Ser Cys Leu Gln Glu Gly Gln Cys Glu Asn Asp
705                 710                 715                 720

Pro Lys Ser Lys Lys Val Ser Asp Ile Lys Glu Glu Val Leu Ala Ala
                725                 730                 735

Ala Cys His Pro Val Gln His Ser Lys Val Glu Tyr Ser Asp Thr Asp
            740                 745                 750

Phe Gln Ser Glu Lys Ser Leu Leu Tyr Asp His Glu Asn Ala Ser Thr
        755                 760                 765

Leu Ile Leu Thr Pro Thr Ser Lys Asp Val Leu Ser Asn Leu Val Met
    770                 775                 780

Ile Ser Arg Gly Lys Glu Ser Tyr Lys Met Ser Asp Lys Leu Lys Gly
785                 790                 795                 800
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Asn Asn Tyr Glu Ser Asp Val Gln Leu Thr Lys Asn Ile Pro Met Glu
                805                 810                 815

Lys Asn Gln Asp Val Cys Ala Leu Asn Glu Asn Tyr Lys Asn Val Glu
            820                 825                 830

Leu Leu Pro Pro Glu Lys Tyr Met Arg Val Ala Ser Pro Ser Arg Lys
        835                 840                 845

Val Gln Phe Asn Gln Asn Thr Asn Leu Arg Val Ile Gln Lys Asn Gln
    850                 855                 860

Glu Glu Thr Thr Ser Ile Ser Lys Ile Thr Val Asn Pro Asp Ser Glu
865                 870                 875                 880

Glu Leu Phe Ser Asp Asn Gln Asn Asn Phe Val Phe Gln Val Ala Asn
                885                 890                 895

Glu Arg Asn Asn Leu Ala Leu Gly Asn Thr Lys Glu Leu His Glu Thr
            900                 905                 910

Asp Leu Thr Cys Val Asn Gln Pro Ile Phe Lys Asn Ser Thr Met Val
        915                 920                 925

Leu Tyr Gly Asp Thr Gly Asp Lys Gln Ala Thr Gln Val Ser Ile Lys
    930                 935                 940

Lys Asp Leu Val Tyr Val Leu Ala Glu Glu Asn Lys Asn Ser Val Lys
945                 950                 955                 960

Gln His Ile Lys Met Thr Leu Gly Gln Asp Leu Lys Ser Asp Ile Ser
                965                 970                 975

Leu Asn Ile Asp Lys Ile Pro Glu Lys Asn Asn Asp Tyr Met Asn Lys
            980                 985                 990

Trp Ala Gly Leu Leu Gly Pro Ile Ser Asn His Ser Phe Gly Gly Ser
        995                 1000                1005

Phe Arg Thr Ala Ser Asn Lys Gln Ile Lys Leu Ser Glu His Asn Ile
    1010                1015                1020

Lys Lys Ser Lys Met Phe Phe Lys Asp Ile Glu Glu Gln Tyr Pro Thr
1025                1030                1035                1040

Ser Leu Ala Cys Val Gln Ile Val Asn Thr Leu Ala Leu Asp Asn Gln
                1045                1050                1055

Lys Lys Leu Ser Lys Pro Glu Ser Ile Asn Thr Val Ser Ala His Leu
            1060                1065                1070

Gln Ser Ser Val Val Val Ser Asp Cys Lys Asn Ser His Ile Thr Pro
        1075                1080                1085

Gln Met Leu Phe Ser Lys Gln Asp Phe Asn Ser Asn His Asn Leu [illegible]
    1090                1095                1100

Pro Ser Gln Lys Ala Glu Ile Thr Glu Leu Ser Thr Ile Leu Glu Glu
1105                1110                1115                1120

Ser Gly Ser Gln Phe Glu Phe Thr Glu Phe Arg Lys Pro Ser Tyr Ile
                1125                1130                1135

Leu Gln Lys Ser Thr Phe Glu Val Pro Glu Asn Gln Met Thr Ile Leu
            1140                1145                1150

Lys Thr Thr Ser Glu Glu Cys Arg Asp Ala Asp Leu His Val Ile Met
        1155                1160                1165

Asn Ala Pro Ser Ile Gly Gln Val Asp Ser Ser Lys Gln Phe Glu Gly
    1170                1175                1180

Thr Val Glu Ile Lys Arg Lys Phe Ala Gly Leu Leu Lys Asn Asp Cys
1185                1190                1195                1200

Asn Lys Ser Ala Ser Gly Tyr Leu Thr Asp Glu Asn Gln Val Gly Phe
                1205                1210                1215
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Arg Gly Phe Tyr Ser Ala His Gly Thr Lys Leu Asn Val Ser Thr Glu
            1220                1225                1230

Ala Leu Gln Lys Ala Val Lys Leu Phe Ser Asp Ile Glu Asn Ile Ser
        1235                1240                1245

Glu Gln Thr Ser Ala Glu Val His Pro Ile Ser Leu Ser Ser Ser Lys
    1250                1255                1260

Cys His Asp Ser Val Val Ser Met Phe Lys Ile Glu Asn His Asn Asp
1265                1270                1275                1280

Lys Thr Val Ser Glu Lys Asn Asn Lys Cys Gln Leu Ile Leu Gln Asn
                1285                1290                1295

Asn Ile Glu Met Thr Thr Gly Thr Phe Val Glu Glu Ile Thr Glu Asn
            1300                1305                1310

Tyr Lys Arg Asn Thr Glu Asn Glu Asp Asn Lys Tyr Thr Ala Ala Ser
        1315                1320                1325

Arg Asn Ser His Asn Leu Glu Phe Asp Gly Ser Asp Ser Ser Lys Asn
    1330                1335                1340

Asp Thr Val Cys Ile His Lys Asp Glu Thr Asp Leu Leu Phe Thr Asp
1345                1350                1355                1360

Gln His Asn Ile Cys Leu Lys Leu Ser Gly Gln Phe Met Lys Glu Gly
                1365                1370                1375

Asn Thr Glu Ile Lys Glu Asp Leu Ser Asp Leu Thr Phe Leu Glu Val
            1380                1385                1390

Ala Lys Ala Gln Glu Ala Cys His Gly Asn Thr Ser Asn Lys Glu Glu
        1395                1400                1405

Leu Thr Ala Thr Lys Thr Glu Gln Asn Ile Lys Asp Phe Glu Thr Ser
    1410                1415                1420

Asp Thr Phe Phe Gln Thr Ala Ser Gly Lys Asn Ile Ser Val Ala Lys
1425                1430                1435                1440

Glu Ser Phe Asn Lys Ile Val Asn Phe Phe Asp Gln Lys Pro Glu Glu
                1445                1450                1455

Leu His Asn Phe Ser Leu Asn Ser Glu Leu His Ser Asp Ile Arg Lys
            1460                1465                1470

Asn Lys Met Asp Ile Leu Ser Tyr Glu Glu Thr Asp Ile Val Lys His
        1475                1480                1485

Lys Ile Leu Lys Glu Ser Val Pro Val Gly Thr Gly Asn Gln Leu Val
    1490                1495                1500

Thr Phe Gln Gly Gln Pro Glu Arg Asp Glu Lys Ile Lys Glu Pro Thr
1505                1510                1515                1520

Leu Leu Gly Phe His Thr Ala Ser Gly Lys Lys Val Lys Ile Ala Lys
                1525                1530                1535

Glu Ser Leu Asp Lys Val Lys Asn Leu Phe Asp Glu Lys Glu Gln Gly
            1540                1545                1550

Thr Ser Glu Ile Thr Ser Phe Ser His Gln Trp Ala Lys Thr Leu Lys
        1555                1560                1565

Tyr Arg Glu Ala Cys Lys Asp Leu Glu Leu Ala Cys Glu Thr Ile Glu
    1570                1575                1580

Ile Thr Ala Ala Pro Lys Cys Lys Glu Met Gln Asn Ser Leu Asn Asn
1585                1590                1595                1600

Asp Lys Asn Leu Val Ser Ile Glu Thr Val Val Pro Pro Lys Leu Leu
                1605                1610                1615

Ser Asp Asn Leu Cys Arg Gln Thr Glu Asn Leu Lys Thr Ser Lys Ser
            1620                1625                1630

Ile Phe Leu Lys Val Lys Val His Glu Asn Val Glu Lys Glu Thr Ala
        1635                1640                1645
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Lys Ser Pro Ala Thr Cys Tyr Thr Asn Gln Ser Pro Tyr Ser Val Ile
    1650                1655                1660

Glu Asn Ser Ala Leu Ala Phe Tyr Thr Ser Cys Ser Arg Lys Thr Ser
1665                1670                1675                1680

Val Ser Glu Thr Ser Leu Leu Glu Ala Lys Lys Trp Leu Arg Glu Gly
                1685                1690                1695

Ile Phe Asp Gly Gln Pro Glu Arg Ile Asn Thr Ala Asp Tyr Val Gly
            1700                1705                1710

Asn Tyr Leu Tyr Glu Asn Asn Ser Asn Ser Thr Ile Ala Gln Asn Asp
        1715                1720                1725

Lys Asn His Leu Ser Glu Lys Gln Asp Thr Tyr Leu Ser Asn Ser Ser
    1730                1735                1740

Met Ser Asn Ser Tyr Ser Tyr His Ser Asp Glu Val Tyr Asn Asp Ser
1745                1750                1755                1760

Gly Tyr Leu Ser Lys Asn Lys Leu Asp Ser Gly Ile Glu Pro Val Leu
                1765                1770                1775

Lys Asn Val Glu Asp Gln Lys Asn Thr Ser Phe Ser Lys Val Ile Ser
            1780                1785                1790

Asn Val Lys Asp Ala Asn Ala Tyr Pro Glu Thr Val Asn Glu Asp Ile
        1795                1800                1805

Cys Val Glu Glu Leu Val Thr Ser Ser Ser Pro Cys Lys Asn Lys Asn
    1810                1815                1820

Ala Ala Ile Lys Leu Ser Ile Ser Asn Ser Asn Asn Phe Glu Val Gly
1825                1830                1835                1840

Pro Pro Ala Phe Arg Ile Ala Ser Gly Lys Ile Val Cys Val Ser His
                1845                1850                1855

Glu Thr Ile Lys Lys Val Lys Asp Ile Phe Thr Asp Ser Phe Ser Lys
            1860                1865                1870

Val Ile Lys Glu Asn Asn Glu Asn Lys Ser Lys Ile Cys Gln Thr Lys
        1875                1880                1885

Ile Met Ala Gly Cys Tyr Glu Ala Leu Asp Asp Ser Glu Asp Ile Leu
    1890                1895                1900

His Asn Ser Leu Asp Asn Asp Glu Cys Ser Thr His Ser His Lys Val
1905                1910                1915                1920

Phe Ala Asp Ile Gln Ser Glu Glu Ile Leu Gln His Asn Gln Asn Met
                1925                1930                1935

Ser Gly Leu Glu Lys Val Ser Lys Ile Ser Pro Cys Asp Val Ser Leu
            1940                1945                1950

Glu Thr Ser Asp Ile Cys Lys Cys Ser Ile Gly Lys Leu His Lys Ser
        1955                1960                1965

Val Ser Ser Ala Asn Thr Cys Gly Ile Phe Ser Thr Ala Ser Gly Lys
    1970                1975                1980

Ser Val Gln Val Ser Asp Ala Ser Leu Gln Asn Ala Arg Gln Val Phe
1985                1990                1995                2000

Ser Glu Ile Glu Asp Ser Thr Lys Gln Val Phe Ser Lys Val Leu Phe
                2005                2010                2015

Lys Ser Asn Glu His Ser Asp Gln Leu Thr Arg Glu Glu Asn Thr Ala
            2020                2025                2030

Ile Arg Thr Pro Glu His Leu Ile Ser Gln Lys Gly Phe Ser Tyr Asn
        2035                2040                2045

Val Val Asn Ser Ser Ala Phe Ser Gly Phe Ser Thr Ala Ser Gly Lys
    2050                2055                2060
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Gln Val Ser Ile Leu Glu Ser Ser Leu His Lys Val Lys Gly Val Leu
2065                2070                2075                2080

Glu Glu Phe Asp Leu Ile Arg Thr Glu His Ser Leu His Tyr Ser Pro
                2085                2090                2095

Thr Ser Arg Gln Asn Val Ser Lys Ile Leu Pro Arg Val Asp Lys Arg
            2100                2105                2110

Asn Pro Glu His Cys Val Asn Ser Glu Met Gln Lys Thr Cys Ser Lys
        2115                2120                2125

Glu Phe Lys Leu Ser Asn Asn Leu Asn Val Glu Gly Gly Ser Ser Glu
    2130                2135                2140

Asn Asn His Ser Ile Lys Val Ser Pro Tyr Leu Ser Gln Phe Gln Gln
2145                2150                2155                2160

Asp Lys Gln Gln Leu Val Leu Gly Thr Lys Val Ser Leu Val Glu Asn
                2165                2170                2175

Ile His Val Leu Gly Lys Glu Gln Ala Ser Pro Lys Asn Val Lys Met
            2180                2185                2190

Glu Ile Gly Lys Thr Glu Thr Phe Ser Asp Val Pro Val Lys Thr Asn
        2195                2200                2205

Ile Glu Val Cys Ser Thr Tyr Ser Lys Asp Ser Glu Asn Tyr Phe Glu
    2210                2215                2220

Thr Glu Ala Val Glu Ile Ala Lys Ala Phe Met Glu Asp Asp Glu Leu
2225                2230                2235                2240

Thr Asp Ser Lys Leu Pro Ser His Ala Thr His Ser Leu Phe Thr Cys
                2245                2250                2255

Pro Glu Asn Glu Glu Met Val Leu Ser Asn Ser Arg Ile Gly Lys Arg
            2260                2265                2270

Arg Gly Glu Pro Leu Ile Leu Val Gly Glu Pro Ser Ile Lys Arg Asn
        2275                2280                2285

Leu Leu Asn Glu Phe Asp Arg Ile Ile Glu Asn Gln Glu Lys Ser Leu
    2290                2295                2300

Lys Ala Ser Lys Ser Thr Pro Asp Gly Thr Ile Lys Asp Arg Arg Leu
2305                2310                2315                2320

Phe Met His His Val Ser Leu Glu Pro Ile Thr Cys Val Pro Phe Arg
                2325                2330                2335

Thr Thr Lys Glu Arg Gln Glu Ile Gln Asn Pro Asn Phe Thr Ala Pro
            2340                2345                2350

Gly Gln Glu Phe Leu Ser Lys Ser His Leu Tyr Glu His Leu Thr Leu
        2355                2360                2365

Glu Lys Ser Ser Ser Asn Leu Ala Val Ser Gly His Pro Phe Tyr Gln
    2370                2375                2380

Val Ser Ala Thr Arg Asn Glu Lys Met Arg His Leu Ile Thr Thr Gly
2385                2390                2395                2400

Arg Pro Thr Lys Val Phe Val Pro Pro Phe Lys Thr Lys Ser His Phe
                2405                2410                2415

His Arg Val Glu Gln Cys Val Arg Asn Ile Asn Leu Glu Glu Asn Arg
            2420                2425                2430

Gln Lys Gln Asn Ile Asp Gly His Gly Ser Asp Asp Ser Lys Asn Lys
        2435                2440                2445

Ile Asn Asp Asn Glu Ile His Gln Phe Asn Lys Asn Asn Ser Asn Gln
    2450                2455                2460

Ala Ala Ala Val Thr Phe Thr Lys Cys Glu Glu Glu Pro Leu Asp Leu
2465                2470                2475                2480

Ile Thr Ser Leu Gln Asn Ala Arg Asp Ile Gln Asp Met Arg Ile Lys
                2485                2490                2495
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Lys Lys Gln Arg Gln Arg Val Phe Pro Glu Pro Gly Ser Leu Tyr Leu
            2500                2505                2510

Ala Lys Thr Ser Thr Leu Pro Arg Ile Ser Leu Lys Ala Ala Val Gly
        2515                2520                2525

Gly Gln Val Pro Ser Ala Cys Ser His Lys Gln Leu Tyr Thr Tyr Gly
    2530                2535                2540

Val Ser Lys His Cys Ile Lys Ile Asn Ser Lys Asn Ala Glu Ser Phe
2545                2550                2555                2560

Gln Phe His Thr Glu Asp Tyr Phe Gly Lys Glu Ser Leu Trp Thr Gly
                2565                2570                2575

Lys Gly Ile Gln Leu Ala Asp Gly Gly Trp Leu Ile Pro Ser Asn Asp
            2580                2585                2590

Gly Lys Ala Gly Lys Glu Glu Phe Tyr Arg Ala Leu Cys Asp Thr Pro
        2595                2600                2605

Gly Val Asp Pro Lys Leu Ile Ser Arg Ile Trp Val Tyr Asn His Tyr
    2610                2615                2620

Arg Trp Ile Ile Trp Lys Leu Ala Ala Met Glu Cys Ala Phe Pro Lys
2625                2630                2635                2640

Glu Phe Ala Asn Arg Cys Leu Ser Pro Glu Arg Val Leu Leu Gln Leu
                2645                2650                2655

Lys Tyr Arg Tyr Asp Thr Glu Ile Asp Arg Ser Arg Arg Ser Ala Ile
            2660                2665                2670

Lys Lys Ile Met Glu Arg Asp Asp Thr Ala Ala Lys Thr Leu Val Leu
        2675                2680                2685

Cys Val Ser Asp Ile Ile Ser Leu Ser Ala Asn Ile Ser Glu Thr Ser
    2690                2695                2700

Ser Asn Lys Thr Ser Ser Ala Asp Thr Gln Lys Val Ala Ile Ile Glu
2705                2710                2715                2720

Leu Thr Asp Gly Trp Tyr Ala Val Lys Ala Gln Leu Asp Pro Pro Leu
                2725                2730                2735

Leu Ala Val Leu Lys Asn Gly Arg Leu Thr Val Gly Gln Lys Ile Ile
            2740                2745                2750

Leu His Gly Ala Glu Leu Val Gly Ser Pro Asp Ala Cys Thr Pro Leu
        2755                2760                2765

Glu Ala Pro Glu Ser Leu Met Leu Lys Ile Ser Ala Asn Ser Thr Arg
    2770                2775                2780

Pro Ala Arg Trp Tyr Thr Lys Leu Gly Phe Phe Pro Asp Pro Arg Pro
2785                2790                2795                2800

Phe Pro Leu Pro Leu Ser Ser Leu Phe Ser Asp Gly Gly Asn Val Gly
                2805                2810                2815

Cys Val Asp Val Ile Ile Glu Arg Ala Tyr Pro Ile Gln Trp Met Glu
            2820                2825                2830

Lys Thr Ser Ser Gly Leu Tyr Ile Phe Arg Asn Glu Arg Glu Glu Glu
        2835                2840                2845

Lys Glu Ala Ala Lys Tyr Val Glu Ala Gln Gln Lys Arg Leu Glu Ala
    2850                2855                2860

Leu Phe Thr Lys Ile Gln Glu Glu Phe Glu Glu His Glu Glu Asn Thr
2865                2870                2875                2880

Thr Lys Pro Tyr Leu Pro Ser Arg Ala Leu Thr Arg Gln Gln Val Arg
                2885                2890                2895

Ala Leu Gln Asp Gly Ala Glu Leu Tyr Glu Ala Val Lys Asn Ala Ala
            2900                2905                2910
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Asp Pro Ala Tyr Leu Glu Gly Tyr Phe Ser Gln Gln Gln Leu Arg Ala
        2915                2920                2925

Leu Asn Asn His Arg Gln Met Leu Asn Asp Lys Lys Gln Ala Gln Ile
    2930                2935                2940

Gln Leu Glu Ile Arg Lys Ala Met Gly Ser Ala Gln Gln Lys Glu Gln
2945                2950                2955                2960

Gly Leu Ser Arg Asp Val Thr Thr Val Trp Lys Leu Arg Ile Val Ser
                2965                2970                2975

Tyr Ser Lys Lys Glu Lys Asp Ser Val Ile Leu Ser Ile Trp Arg Pro
            2980                2985                2990

Ser Ser Asp Leu Tyr Ser Leu Leu Thr Glu Gly Lys Arg Tyr Arg Ile
        2995                3000                3005

Tyr His Leu Ala Thr Ser Lys Ser Lys Ser Lys Ser Glu Arg Ala Asn
    3010                3015                3020

Ile Gln Leu Ala Ala Thr Lys Lys Thr Gln Tyr Glu Gln Leu Pro Val
3025                3030                3035                3040

Ser Asp Gln Ile Leu Phe Gln Ile Tyr Gln Pro Arg Gln Pro Leu His
                3045                3050                3055

Phe Ser Lys Phe Leu Asp Pro Asp Phe Gln Pro Ser Cys Ser Glu Val
            3060                3065                3070

Asp Leu Ile Gly Phe Val Val Ser Val Val Lys Lys Thr Gly Leu Ala
        3075                3080                3085

Pro Phe Val Tyr Leu Ser Asp Gln Cys Tyr Asn Leu Leu Ala Ile Lys
    3090                3095                3100

Phe Trp Ile Asp Leu Asn Glu Asp Ile Ile Lys Pro His Met Leu Ile
3105                3110                3115                3120

Ala Ala Ser Asn Leu Gln Trp Arg Pro Glu Ser Lys Ser Gly Leu Leu
                3125                3130                3135

Thr Leu Phe Ala Gly Asp Phe Ser Val Phe Ser Ala Ser Pro Lys Gly
            3140                3145                3150

Gly His Phe Gln Glu Thr Phe Asn Lys Met Lys Asn Thr Val Glu Asn
        3155                3160                3165

Ile Asp Ile Leu Cys Asn Glu Ala Gln Asn Lys Leu Met His Ile Leu
    3170                3175                3180

His Ala Asn Asp Pro Lys Trp Ser Thr Pro Thr Lys Asp Cys Thr Ser
3185                3190                3195                3200

Gly Pro Tyr Thr Ala Gln Ile Ile Pro Gly Thr Gly Asn Lys Leu Leu
                3205                3210                3215

Met Ser Ser Pro Asn Cys Glu Ile Tyr Tyr Gln Ser Pro Leu Ser Leu
            3220                3225                3230

Cys Met Ala Lys Arg Lys Ser Val Ser Thr Pro Val Ser Ala Gln Met
        3235                3240                3245

Thr Ser Lys Ser Cys Lys Gly Glu Lys Glu Ile Asp Asp Gln Lys Asn
    3250                3255                3260

Cys Lys Lys Arg Arg Ala Leu Asp Phe Leu Ser Arg Leu Pro Leu Pro
3265                3270                3275                3280

Pro Pro Val Ser Pro Ile Cys Thr Phe Val Ser Pro Ala Ala Glu Lys
                3285                3290                3295

Ala Phe Gln Pro Pro Arg Ser Cys Gly Thr Lys Tyr Glu Thr Pro Ile
            3300                3305                3310

Lys Lys Lys Glu Leu Asn Ser Pro Gln Met Thr Pro Phe Lys Lys Phe
        3315                3320                3325

Asn Glu Ile Ser Leu Leu Glu Ser Asn Ser Ile Ala Asp Glu Glu Leu
    3330                3335                3340
```

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Ala Leu Ile Asn Thr Gln Ala Leu Leu Ser Gly Ser Thr Gly Gln Lys
3345                3350                3355                3360

Gln Phe Ile Ser Val Ser Glu Ser Thr Arg Thr Ala Pro Thr Ser Ser
                3365                3370                3375

Gln Asp Tyr Leu Arg Leu Lys Arg Arg Cys Thr Thr Ser Leu Ile Lys
            3380                3385                3390

Glu Gln Glu Ser Ser Gln Ala Ser Thr Glu Glu Cys Glu Lys Asn Lys
        3395                3400                3405

Gln Asp Thr Ile Thr Thr Lys Lys Tyr Ile
    3410                3415
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 32 base pairs
  (B) TYPE: nucleic acid
  (C) STRANDEDNESS: single
  (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
  (A) ORGANISM: Homo sapiens

(i x) FEATURE:
  (A) NAME/KEY: misc_feature
  (B) LOCATION: 1..2
  (D) OTHER INFORMATION: /note= "(NH2) at nucleotide 1"

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:3:

GTAGTCCAAG GCTCGAGAAC NNNNNNNNNN NN 32

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 30 base pairs
  (B) TYPE: nucleic acid
  (C) STRANDEDNESS: single
  (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
  (A) DESCRIPTION: /desc = "primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
  (A) ORGANISM: Homo sapiens

(i x) FEATURE:
  (A) NAME/KEY: misc_feature
  (B) LOCATION: 1..2
  (D) OTHER INFORMATION: /note= "(NH2) at nucleotide 1"

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:4:

TCAGTAGAAT TCTAACGGCC GTCATTGTTC 30

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 30 base pairs
  (B) TYPE: nucleic acid
  (C) STRANDEDNESS: single
  (D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(i x) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 29..30
(D) OTHER INFORMATION: /note= "(NH2) at nucleotide 30"

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GAACAATGAC GGCCGTTAGA ATTCTACTCA 30

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:6:

TCAGTAGAAT TCTAACGGCC GTCAT 25

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(i x) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1..2
(D) OTHER INFORMATION: /note= "(PO4) at nucleotide 1"

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GTAGTCCAAG GCTCGAGAAC 20

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid

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(A) DESCRIPTION: /desc = "primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(i x) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1..2
(D) OTHER INFORMATION: /note= "(PO4) at nucleotide 1"

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:8:

TCAGTACAAT TCTAACGGCC GTCATTC 27

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(i x) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 32..33
(D) OTHER INFORMATION: /note= "(NH2) at nucleotide 33"

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:9:

CCTTCACACG CGTATCGATT AGTCACNNNN NNN 33

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(i x) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1..2
(D) OTHER INFORMATION: /note= "(PO4) at nucleotide 1"

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:10:

GTGACTAATC GATACGCGTG TGAAGGTGC 29

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid

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(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(i x) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1..2
(D) OTHER INFORMATION: /note= "Biotinylated at nucleotide 1"

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:11:

TTGAAGAACA ACAGCACTTT CACTA 25

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:12:

CACCTTCACA CGCCTATCG 19

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GTTCGTAATT GTTCTTTTTA TGTTCAG 27

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "primer"

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(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:14:

CCTTCACACG CGTATCGATT AG 22

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:15:

TTTGGATCAT TTTCACACTG TC 22

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:16:

GTGCTCATAG TCAGAAATGA AG 22

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:17:

TCTTCCCATC CTCACAGTAA G 21

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:18:

CTACTGGGTT TTTAGCAAGC A 21

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GGTTAAAACT AAGGTGGGA 19

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:20:

ATTTGCCCAG CATGACACA 19

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

-continued

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:21:

TTTCCCAGTA TAGAGGAGA 19

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:22:

GTAGGAAAAT GTTTCATTTA A 21

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:23:

ATCTAAAGTA GTATTCCAAC A 21

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GGGGGTAAAA AAAGGGGAA 19

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid

-continued

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:25:

GAGATAAGTC AGGTATGATT 20

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:26:

AATTGCCTGT ATGAGGCAGA 20

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:27:

GGCAATTCAG TAAACGTTAA 20

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:28:

-continued

ATTGTCAGTT ACTAACACAC 20

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GTGTCATGTA ATCAAATACT 20

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:30:

CAGGTTTAGA GACTTTCTC 19

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:31:

GGACCTAGGT TGATTGCA 18

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:32:

GTCAAGAAAG GTAAGGTAA 19

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CTATGAGAAA GGTTGTGAG 19

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:34:

CCTAGTCTTG CTAGTTCTT 19

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:35:

AACAGTTGTA GATACCTCTG AA 22

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

-continued

(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GACTTTTTGA TACCCTGAAA TG 22

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:37:

CAGCATCTTG AATCTCATAC AG 22

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:38:

CATGTATACA GATGATGCCT AAG 23

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:39:

AACTTAGTCA AAAATATTTA GTGA 24

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:40:

ATACATCTTG ATTCTTTTCC AT 22

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:41:

TTTAGTCAAT GTCATTCATG GT 22

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:42:

AGAACCAACT TTGTCCTTAA 20

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

-continued

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:43:

TTAGATTTGT GTTTTGGTTG AA 22

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:44:

TAGCTCTTTT GGGACAATTC 20

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:45:

ATGCAAAAGA ATCAAGATGT AT 22

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:46:

CCTAATGTTA TGTTCAGAGA G 21

(2) INFORMATION FOR SEQ ID NO:47:

-continued

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:47:

GCTACCTCCA AAACTGTCA 19

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:48:

GTGTAAAGCA GCATATAAAA AT 22

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:49:

CTTGCTGCTG TCTACCTG 18

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:

-continued

(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:50:

AGTGGTCTTA AGATAGTCAT 20

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:51:

CCATAATTTA ACACCTAGCC A 21

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:52:

CCAAAAAAGT TAAATCTCAC A 21

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:53:

GGCTTTTATT CTGCTCATGG C 21

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

-continued

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:54:

CCTCTGCAGA AGTTTCCTCA C 21

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:55:

AACCGACTTG CTATTTACTG A 21

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:56:

ACTACCTTGC TCTTTTTCAT C 21

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:57:

CAGCTAGCCG GAAAAAAGTT A 21

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:58:

TTCCCAGACA TGATTTTTGT C 21

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:59:

GCCTTAGCTT TTTACACAA 19

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:60:

TTTTTGATTA TATCTCGTTG 20

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:61:

TTATTCTCGT TGTTTTCCTT A 21

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:62:

CCATTAAATT GTCCATATCT A 21

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:63:

GACCTAGGTG AATACTGAAG A 21

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:64:

TCAAATTCCT CTAACACTCC 20

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: *Homo sapiens*

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:65:

GAAGATACTA CCAAGCAAGT C 21

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: *Homo sapiens*

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:66:

TGAGACTTTG GTTCCTAATA C 21

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: *Homo sapiens*

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:67:

AGTAACGAAC ATTCAGACCA G 21

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: *Homo sapiens*

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:68:

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GTCTTCACTA TTCACCTACG 20

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:69:

CCCCCAAACT GACTACACAA 20

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:70:

ACCATACCAA CTCTACTGAA T 21

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:71:

ACTCTTTCAA ACATTAGCTC A 21

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

-continued

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: *Homo sapiens*

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:72:

TTGGAGAGCC AGGTGGAT 18

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: *Homo sapiens*

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:73:

CTATAGAGGG AGAACAGAT 19

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: *Homo sapiens*

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:74:

TTTATGCTGA TTTCTGTTGT AT 22

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: *Homo sapiens*

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:75:

ATAAAACGGG AAGTGTTAAC T 21

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:

-continued

(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:76:

CTGTCAGTTA TTTGCTGCAT 20

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:77:

GAATACAAAA CAGTTACCAG A 21

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:78:

CACCACCAAA GGGGGAAA 18

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

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(x i) SEQUENCE DESCRIPTION: SEQ ID NO:79:

AAATGAGGGT CTGCAACAAA 20

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:80:

GTCCCACCAG AACTTGAG 18

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:81:

AGCCATTTGT AGGATACTAG 20

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:82:

CTACTAGACC GGCGGAG 17

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:83:

ATGTTTTTGT AGTGAAGATT CT 22

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:84:

TAGTTCGAGA GACAGTTAAG 20

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:85:

CAGTTTTGGT TTGTTATAAT TG 22

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:86:

CAGAGAATAC TTGTAGTTGT T 21

(2) INFORMATION FOR SEQ ID NO:87:

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(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:87:

AACCTTAACC CATACTGCC 19

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:88:

TTCAGTATCA TCCTATGTGG 20

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:89:

TTTTATTCTC AGTTATTCAG TG 22

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:

-continued

(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:90:

GAAATTGAGC ATCCTTAGTA A 21

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:91:

AATTCTAGAG TCACACTTCC 20

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:92:

ATATTTTTAA GGCACTTCTA CA 22

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:93:

TTACACACAC CAAAAAAGTC A 21

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:94:

TGAAAACTCT TATGATATCT GT 22

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:95:

TGAATGTTAT ATATGTGACT TTT 23

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:96:

CTTGTTGCTA TTCTTTGTCT A 21

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:97:

CCCTAGATAC TAAAAAATAA AG 22

-continued

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:98:

CTTTTAGCAG TTATATAGTT TC 22

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:99:

GCCAGAGAGT CTAAAACAG 19

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:100:

CTTTGGGTGT TTTATGCTTG 20

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:101:

TTTGTTGTAT TTGTCCTGTT TA 22

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:102:

ATTTTGTTAG TAAGGTCATT TTT 23

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:103:

GTTCTGATTG CTTTTTATTC C 21

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:104:

ATCACTTCTT CCATTGCATC 20

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:105:

CCGTGGCTGG TAAATCTG 18

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:106:

CTGGTAGCTC CAACTAATC 19

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:107:

ACCGGTACAA ACCTTTCATT G 21

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:108:

-continued

CTATTTTGAT TTGCTTTTAT TATT 24

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:109:

GCTATTTCCT TGATACTGGA C 21

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:110:

TTGGAAACAT AAATATGTGG G 21

(2) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:111:

ACTTACAGGA GCCACATAAC 20

(2) INFORMATION FOR SEQ ID NO:112:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:112:

CTACATTAAT TATGATAGGC TCG 23

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:113:

GTACTAATGT GTGGTTTGAA A 21

(2) INFORMATION FOR SEQ ID NO:114:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (genomic)

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(v i) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:114:

TCAATGCAAG TTCTTCGTCA GC 22

(2) INFORMATION FOR SEQ ID NO:115:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "Primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:115:

GGGAAGCTTC ATAAGTCAGT C 21

(2) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid

-continued

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "Primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: YES

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:116:

TTTGTAATGA AGCATCTGAT ACC 23

(2) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "Primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:117:

AATGATGAAT GTAGCACGC 19

(2) INFORMATION FOR SEQ ID NO:118:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "Primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: YES

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:118:

GTCTGAATGT TCGTTACT 18

(2) INFORMATION FOR SEQ ID NO:119:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "Primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:119:

ACCATCAAAC ACATCATCC 19

(2) INFORMATION FOR SEQ ID NO:120:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid

-continued

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "Primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: YES

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:120:

AGAAAGTAAC TTGGAGGGAG 20

(2) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "Primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:121:

CTCCTGAAAC TGTTCCCTTG G 21

(2) INFORMATION FOR SEQ ID NO:122:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "Primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: YES

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:122:

TAATGGTGCT GGGATATTTG G 21

(2) INFORMATION FOR SEQ ID NO:123:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "Primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:123:

GAATGTCGAA GAGCTTGTC 19

(2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid

-continued

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "Primer"

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: YES

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:124:

AAACATACGC TTAGCCAGAC 20

What is claimed is:

1. An isolated DNA molecule coding for a BRCA2 polypeptide, said DNA molecule comprising a nucleic acid sequence encoding the amino acid sequence set forth in SEQ ID NO:2.

2. The isolated DNA molecule of claim 1, wherein said DNA molecule comprises the nucleotide sequence set forth in SEQ ID NO:1.

3. The isolated DNA molecule of claim 1, wherein said DNA molecule is an allelic variant of the nucleotide sequence set forth in SEQ ID NO:1.

4. The isolated DNA molecule of claim 1, which contains BRCA2 regulatory sequences.

5. An isolated DNA molecule comprising at least 15 contiguous nucleotides of the DNA molecule of claim 1.

6. An isolated DNA molecule coding for a mutated form of the BRCA2 polypeptide set forth in SEQ ID NO:2, wherein said mutated form of the BRCA2 polypeptide is associated with susceptibility to cancer.

7. The isolated DNA molecule of claim 6, wherein the DNA molecule comprises a mutated nucleotide sequence set forth in SEQ ID NO:1.

8. The isolated DNA molecule of claim 7, wherein the mutation is selected from the group consisting of a deletion mutation, a nonsense mutation, an insertion mutation and a missense mutation.

9. An isolated DNA molecule comprising at least 15 contiguous nucleotides of the DNA of claim 6.

10. The isolated DNA molecule of claim 6 selected from the group consisting of:

(a) SEQ ID NO:1 having AC at nucleotide positions 277 and 278 deleted;

(b) SEQ ID NO:1 having four nucleotides at positions 982–985 deleted;

(c) SEQ ID NO:1 having four nucleotides at positions 4706–4709 deleted;

(d) SEQ ID NO:1 having C at nucleotide position 8525 deleted;

(e) SEQ ID NO:1 having five nucleotides at positions 9254–9258 deleted;

(f) SEQ ID NO:1 having GT at nucleotide positions 4075 and 4076 deleted;

(g) SEQ ID NO:1 having five nucleotides at positions 999–1003 deleted;

(h) SEQ ID NO:1 having T at nucleotide position 6174 deleted;

(i) SEQ ID NO:1 having three nucleotides at positions 4132–4134 deleted;

(j) SEQ ID NO:1 having a C instead of a G at position 451;

(k) SEQ ID NO:1 having a C instead of an A at position 1093;

(l) SEQ ID NO:1 having a C instead of a G at position 1291;

(m) SEQ ID NO:1 having A at position 1493 deleted;

(n) SEQ ID NO:1 having a T instead of a C at position 2117;

(o) SEQ ID NO:1 having a C instead of an A at position 2411;

(p) SEQ ID NO:1 having an A instead of a G at position 4813;

(q) SEQ ID NO:1 having a G instead of a T at position 5868;

(r) SEQ ID NO:1 having a T instead of a C at position 5972;

(s) SEQ ID NO:1 having a T instead of a C at position 6328;

(t) SEQ ID NO:1 having a T instead of a G at position 7049;

(u) SEQ ID NO:1 having a C instead of a G at position 7491;

(v) SEQ ID NO:1 having a G instead of an A at position 9537;

(w) SEQ ID NO:1 having a T instead of an A at position 10204;

(x) SEQ ID NO:1 having a G instead of a C at position 10298;

(y) SEQ ID NO:1 having a G instead of an A at position 10462;

(z) SEQ ID NO:1 having an A instead of a G at position 203;

(aa) SEQ ID NO:1 having an A instead of a C at position 1342;

(bb) SEQ ID NO:1 having a C instead of a T at position 2457;

(cc) SEQ ID NO:1 having a G instead of an A at position 3199;

(dd) SEQ ID NO:1 having a G instead of an A at position 3624;

(ee) SEQ ID NO:1 having a G instead of an A at position 3668;

(ff) SEQ ID NO:1 having a C instead of a T at position 4035;

(gg) SEQ ID NO:1 having a G instead of an A at position 7470;

(hh) SEQ ID NO:1 having a G instead of an A at position 1593;

(ii) SEQ ID NO:1 having an A instead of a G at position 4296;

(jj) SEQ ID NO:1 having a G instead of an A at position 5691;

(kk) SEQ ID NO:1 having a G instead of an A at position 6051;

(ll) SEQ ID NO:1 having a C instead of a T at position 6828; and

(mm) SEQ ID NO:1 having a C instead of a T at position 6921.

11. A replicative cloning vector which comprises the isolated DNA molecule of claim 1, or at least 15 contiguous nucleotides of the isolated DNA molecule of claim 1, and a replicon operative in a host cell.

12. A replicative cloning vector which comprises the isolated DNA molecule of claim 2, or at least 15 contiguous nucleotides of the isolated DNA molecule of claim 2, and a replicon operative in a host cell.

13. A replicative cloning vector which comprises the isolated DNA molecule of claim 3, or at least 15 contiguous nucleotides of the isolated DNA molecule of claim 3, and a replicon operative in a host cell.

14. A replicative cloning vector which comprises the isolated DNA molecule of claim 6, or at least 15 contiguous nucleotides of the isolated DNA molecule of claim 6, and a replicon operative in a host cell.

15. A replicative cloning vector which comprises the isolated DNA molecule of claim 7, or at least 15 contiguous nucleotides of the isolated DNA molecule of claim 7, and a replicon operative in a host cell.

16. An expression vector which comprises the isolated DNA of claim 1, or at least 15 contiguous nucleotides of the isolated DNA molecule of claim 1, operably linked to transcription regulatory regions.

17. An expression vector which comprises the isolated DNA of claim 2, or at least 15 contiguous nucleotides of the isolated DNA molecule of claim 2, operably linked to transcription regulatory regions.

18. An expression vector which comprises the isolated DNA of claim 3, or at least 15 contiguous nucleotides of the isolated DNA molecule of claim 3, operably linked to transcription regulatory regions.

19. An expression vector which comprises the isolated DNA of claim 6, or at least 15 contiguous nucleotides of the isolated DNA molecule of claim 6, operably linked to transcription regulatory regions.

20. An expression vector which comprises the isolated DNA of claim 7, or at least 15 contiguous nucleotides of the isolated DNA molecule of claim 7, operably linked to transcription regulatory regions.

21. An isolated host cell transformed with the expression vector of claim 16.

22. An isolated host cell transformed with the expression vector of claim 17.

23. An isolated host cell transformed with the expression vector of claim 18.

24. An isolated host cell transformed with the expression vector of claim 19.

25. An isolated host cell transformed with the expression vector of claim 20.

26. A method of producing recombinant BRCA2 polypeptide which comprises culturing the cells of claim 21 under conditions effective for the production of said BRCA2 polypeptide and harvesting the recombinant BRCA2 polypeptide.

27. A method of producing recombinant BRCA2 polypeptide which comprises culturing the cells of claim 22 under conditions effective for the production of said BRCA2 polypeptide and harvesting the recombinant BRCA2 polypeptide.

28. A method of producing recombinant BRCA2 polypeptide which comprises culturing the cells of claim 23 under conditions effective for the production of said BRCA2 polypeptide and harvesting the recombinant BRCA2 polypeptide.

29. A pair of single-stranded DNA primers of at least 15 nucleotides in length for determination of the nucleotide sequence of a BRCA2 gene by a polymerase chain reaction, the sequence of said primers being isolated from human chromosome 13, wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA comprising all or at least 15 contiguous nucleotides of the BRCA2 gene.

30. The pair of primers of claim 29 wherein said BRCA2 gene has the nucleotide sequence set forth in SEQ ID NO:1.

* * * * *

PETITIONER'S BRIEF

RECORD
AND
BRIEFS

No. 12-398

Supreme Court, U.S.
FILED
JAN 2 4 2013
OFFICE OF THE CLERK

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,

Petitioners,

—v.—

MYRIAD GENETICS, INC., ET AL.,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES
COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR PETITIONERS

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QUESTION PRESENTED

Many patients seek genetic testing to see if they have mutations in their genes that are associated with a significantly increased risk of breast or ovarian cancer. Respondent Myriad Genetics obtained patents on two human genes that correlate to this risk, known as BRCA1 and BRCA2. These patents claim every naturally-occurring version of those genes, including mutations, on the theory that Myriad invented something patent-eligible simply by removing ("isolating") the genes from the body. Petitioners are primarily medical professionals who regularly use routine, conventional genetic testing methods to examine genes, but are prohibited from examining the human genes that Myriad claims to own.

The question presented is: Are human genes patentable?

LIST OF PARTIES

The petitioners are the Association for Molecular Pathology, American College of Medical Genetics and Genomics, American Society for Clinical Pathology, College of American Pathologists, Haig Kazazian, MD, Arupa Ganguly, PhD, Wendy Chung, MD, PhD, Harry Ostrer, MD, David Ledbetter, PhD, Stephen Warren, PhD, Ellen Matloff, M.S., Elsa Reich, M.S., Breast Cancer Action, Boston Women's Health Book Collective, Lisbeth Ceriani, Runi Limary, Genae Girard, Patrice Fortune, Vicky Thomason, and Kathleen Raker. The respondents are Myriad Genetics, Inc., and in their official capacity as directors of the University of Utah Research Foundation, Lorris Betz, Roger Boyer, Jack

Brittain, Arnold B. Combe, Raymond Gesteland, James U. Jensen, John Kendall Morris, Thomas Parks, David W. Pershing, and Michael K. Young. The United States Patent and Trademark Office (PTO) was dismissed as a defendant by the district court and that ruling was not appealed. Accordingly, the PTO is not a respondent here.

RULE 29.6 CORPORATE DISCLOSURE STATEMENT

Petitioners do not have any parent corporations, and no publicly held company owns 10 percent or more of the stock of any Petitioner.

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OPINIONS AND ORDERS BELOW

The order of this Court granting certiorari is reported at 133 S. Ct. 694 (2012). The opinion of the U.S. Court of Appeals for the Federal Circuit following remand from this Court is reported at 689 F.3d 1303 (Fed. Cir. 2012) (Pet. App. 2a-119a). This Court's order granting certiorari, vacating, and remanding in light of *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* is reported at 132 S. Ct. 1794 (2012) (Pet. App. 1a). The Federal Circuit's original decision is reported at 653 F.3d 1329 (Fed. Cir. 2011) (Pet. App. 120a-231a). The district court opinion granting summary judgment to Petitioners and denying summary judgment to Respondents is reported at 702 F. Supp. 2d 181 (S.D.N.Y. 2010) (Pet. App. 232a-357a). An earlier opinion of the district court denying the motion to dismiss based, in part, on standing is reported at 669 F. Supp. 2d 365 (S.D.N.Y. 2009) (Pet. App. 358a-425a).

JURISDICTIONAL STATEMENT

The Federal Circuit's decision in this case following remand was issued on August 16, 2012, and this Court granted a timely petition for certiorari on November 30, 2012. Jurisdiction is conferred by 28 U.S.C. § 1254(1).

STATUTORY PROVISION

35 U.S.C. § 101 provides: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."

INTRODUCTION

Human genes are, of course, products of nature. Genetic variants, including mutations, are also products of nature. How genes work and whether variants are harmful or not are laws of nature. Respondents Myriad Genetics *et al.* did not invent any genes or variants or cause their significance, but they did obtain patent claims on two naturally-occurring human genes known as BRCA1 and BRCA2 (so named because one of the diseases to which the genes are linked is breast cancer). The claims are not limited to any form, variation, or structure of the BRCA1 or BRCA2 genes, and they cover the BRCA genes of every person in the United States, even genes that Myriad has never seen.

Myriad defends its claims on the grounds that a gene becomes a human invention when removed from the human body ("isolated"). Under this rationale, a kidney "isolated" from the body would be patentable, gold "isolated" from a stream would be patentable, and leaves "isolated" from trees would be patentable. This defense defies common sense and elevates the draftsman's art over the long-standing prohibition on patenting of products and laws of nature.

Because it is not possible to study or use the genes unless they are isolated, the claims have significant implications. The claims preempt any use of the genes for any purpose. This has serious and urgent consequences for patients today, who often cannot obtain information about their own genes and thus cannot make educated medical decisions about breast and ovarian cancer surveillance and treatment. Myriad has a monopoly on clinical testing of *its* genes in the U.S., dictating the type and terms of BRCA genetic testing. Myriad has given women false negative results, while also barring other laboratories from testing genes to verify the accuracy of Myriad's results. Although Myriad has not exercised its authority to stop all research, Myriad's claims have had a proven chilling effect on research, as laboratories are dissuaded from pursuing scientific work that requires using the patented genes.

Even more disturbingly, because the claims reach all possible uses of the claimed genes, Myriad is authorized to block avenues of scientific inquiry. Myriad can prevent researchers from determining if mutations on the genes correlate with increased risk of other diseases. It can prevent researchers from determining whether the genes could be used in therapy, and if they could, Myriad can prevent that use or lay claim to it. Myriad can stop the development of new types of clinical testing of the genes that take advantage of recent scientific insights. If it were determined that the genes could be used for purposes not now known, such as a substitute for silicon chips in computers (a use currently being explored by companies), Myriad can prevent that use. Myriad can even prevent scientists from looking at their own genes.

This case does not involve a challenge to the method for removing BRCA1 and BRCA2 from the body, nor the process of testing the genes for mutations, nor any drugs developed as a result of scientific research involving the genes. The only question presented by this case is whether human genes can themselves be patented. Because the patents grant exclusive rights over natural phenomena and create barriers to scientific progress and medical care, they must be held invalid.

STATEMENT OF THE CASE

The district court's opinion contains an extensive discussion of the science of DNA and genes, which was supplemented by the Circuit opinions. Pet. App. 254a-72a, 13a-20a.

a. *Nature of Human Genes and DNA*

Every human body contains genes that determine, in part, the structure and functions of the body. Pet. App. 255a-56a, 258a-59a; 1J.A. 130-31, 227-28. The structure and function of human genes are created by nature. Pet. App. 259-260a; 1J.A. 58-59, 63, 91-92, 130-31, 133, 135, 224-25, 232, 234-35, 264, 274-75, 688-89, 703-04, 707.

A gene is a segment of chromosomal DNA. Pet. App. 258a; 1J.A. 229-230.[1] DNA is composed of four repeating elements called nucleotides or bases. Pet. App. 257a. The nucleotides are products of nature. 1J.A. 132.

A gene is defined based on its naturally-occurring qualities. "Each gene is typically thousands of nucleotides long and usually 'encodes' one or more proteins, meaning it contains the information used by the body to produce those proteins." Pet. App. 258a. Nucleotides are represented by four letters, standing for each of the four nucleotides that make up DNA: A (adenine), C (cytosine), T (thymine), and G (guanine). Pet. App. 257a. The linear order of the nucleotides is referred to as the nucleotide sequence or gene sequence or DNA sequence. Pet. App. 259a. The gene sequence is a product of nature and its role in creating proteins (polypeptides) is a law of nature. Pet. App. 260a.

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[1] Because genes are simply segments of DNA, references to DNA in this brief are, unless otherwise noted, references to a DNA segment that constitutes the BRCA1 or BRCA2 genes.

Genes are chemicals, but they are unique because they are much more; they embody the information and instructions the body uses to function. Pet. App. 259a-60a, 355a-56a; 1J.A. 58-59, 130-33, 135-36, 232, 234-35, 561-62, 649-50, 680-81. They determine which polypeptides (proteins) will be made to do the work of the body. Pet. App. 258a, 266a-67a; 1J.A. 132-33, 227-30. Genes "define physical traits such as skin tone, eye color, and sex, in addition to influencing the development of conditions such as obesity, diabetes, Alzheimer's disease and bipolar disorder." Pet. App. 259a. The genes themselves embody laws of nature and the processes by which genes do these things are laws of nature. Pet. App. 257a-62a, 334a-37a; 1J.A. 229-30.

Genes vary from one individual to another. Genetic variants can be inherited or can develop after birth, but the process by which the changes occur is a law of nature and the resultant variant gene is a product of nature. Pet. App. 260a-61a, 270a, 378a; 1J.A. 38-45, 132-33,135-36, 224, 230-31. Genetic variants can be as small as a single deletion (ATAG becomes ATG) or single substitution (ATAG becomes CTAG). Pet. App. 260a-61a. They can also be large with the "addition or deletion of substantial chromosomal regions." Pet. App. 261a. Genetic variants can also "involv[e] the deletion or duplication of up to millions of nucleotides." Pet. App. 261a. Variation in the human genome is very common. Pet. App. 260a; 1J.A. 230. There is not one gene that is "normal," with a few individuals having variants; much variation exists in the genes from one person to another. 1J.A. 230. Myriad claims every version of the BRCA1 gene, but lists just one version in the patents. Patent '282, FIG 10, 2J.A. 738-45. The capital letters in FIG 10 represent the nucleotides called "coding" and the lower case letters represent nucleotides called "non-coding," because they are thought to be unnecessary in the creation of the protein.

Variants can appear to be unimportant, correlate with an increased risk of disease or disorder ("mutations"), or have unknown significance ("variant of uncertain significance"). Pet. App. 18a, 261a; 1J.A. 231-32. The significance of the variant is created entirely by nature. Pet. App. at 270a; 1J.A. 58-59, 135-36, 224, 231-32.

Some mutations in the BRCA1 or BRCA2 genes correlate with an increased risk of breast and/or ovarian cancer. Pet. App. 20a, 278a, 309-310a; Patent '282, 1:20-30, 2J.A. 746. "Women with BRCA1 and BRCA2 mutations face up to an 85% cumulative risk of breast cancer as well as an up to 50% cumulative risk of ovarian cancer. . . . The existence of BRCA1 or BRCA2 mutations is therefore an important consideration in the provision of clinical care for breast and/or ovarian cancer." Pet. App. 278a; 1J.A. 205-06. As the district court found "mutations, along with any association with a propensity to develop a particular disease, are caused by nature. Therefore, the significance of any person's gene sequence, including its relationship to any disease, is dictated by nature." Pet. App. 270a.

b. *Scientific Uses of Genes*

It is useful for pathologists, clinical laboratory scientists, other medical professionals, and researchers to conduct genetic testing for clinically significant alterations. Pet. App. 18a, 263a, 270a-72a, 378a, 380-81a; 1J.A. 58-59, 132-33, 209-10, 232. Sequencing methods are used to examine the precise order of the gene's nucleotides. Pet. App. 259a-60a, 263a, 270a-72a; 1J.A. 58-59, 133-35, 209-10, 223, 232-35; 2J.A. 854. Thousands of medical professionals around the world sequence genes daily, and the processes by which sequencing is done are not at issue here. Pet. App. 272a, 379a; 1J.A. 58-59, 125-26, 133-136, 218, 223, 232, 234-35. At the end of the sequencing process, the medical professional has a long string of the four letters (A, C, T, and G) that correspond to the four nucleotides. Pet. App. 257a, 378a; 1J.A. 58-59, 131-32, 230, 232. The structure, function, and sequence of the nucleotides are created entirely by nature. Pet. App. 260a, 343a; 1J.A. 234-35, 644-46, 653-54, 676, 688-89. After sequencing, the medical professional looks to see if there are variants; *e.g.*, whether natural processes have caused there to be a C where a T would commonly be. 1J.A. 58-59, 135-36, 232. *See, e.g.*, Pet. App. 426a (Patent '282, cl. 7(a)).

Myriad's patent claims have prevented labs other than Myriad from sequencing the BRCA1 and BRCA2 genes and looking to see if there are mutations, actions that are crucial to women and their families facing hereditary breast and ovarian cancer risk. *E.g.*, 1J.A. 60, 87-89, 219-220. In many cases, the effect has been devastating. Some women have obtained testing from Myriad that gave them false negative results because Myriad did not include certain mutations in its standard testing. Tom Walsh et al., *Spectrum of Mutations in BRCA1, BRCA2, Chek2, and TP53 in Families at High Risk of Breast Cancer*, 295 J. Am. Med. Ass'n 1379, 1385-86 (2006). Women and their families make life-changing decisions based on testing provided by one company, without the option of seeking a second opinion. *See id.*; *see also* 1J.A. 76, 78-79, 119. District court plaintiffs Ceriani and Fortune, both breast cancer patients, sought critical testing recommended by their doctors but were denied when Myriad would not accept their insurance. 1J.A. 121-22, 118-119. Plaintiffs Raker and Thomason needed more extensive testing than offered by Myriad's standard test to screen for additional BRCA mutations but Myriad charged prohibitively for that testing. 1J.A. 75, 70-71. All of the plaintiff geneticists were willing to perform the tests for free or for an affordable cost but were prevented from doing so by Myriad's patent claims. *E.g.*, 1J.A. 60, 88-89, 221-22.

But because the patent claims are not limited to the use of the genes in BRCA1 or BRCA2 testing, the effects have been far greater. The patent claims have deterred research as other researchers, including plaintiffs Harry Ostrer, Wendy Chung, and David Ledbetter, are chilled from engaging in scientific work using these genes. 1J.A. 144-48, 220, 714-18. Plaintiff Runi Limary was told by Myriad that she has a "variant of uncertain significance," a result that only Myriad can further explain given their control over patients' BRCA genetic information. 1J.A. 81-83; *see also* 1J.A. 61-62, 91, 113-14, 206-09, 222-23. And the research that has been deterred or prevented is not limited to research into breast and ovarian cancer, but to any research on these genes and their effects.

It is not currently possible to use genes, including looking at or sequencing them, without removing or "isolating" them from the body. Pet. App. 271a, 342a. The isolated gene, however, is not "markedly different" in either structure or function from a gene in the body. Most importantly, the nucleotides that make up DNA – or DNA's "information content" – remain the same. Pet. App. 270a. If that were not the case, Myriad's diagnostic use of the gene would be futile. After isolating and sequencing the gene utilizing conventional methods, Myriad reports to the person who provided the sample that the gene in the body does or does not have a harmful mutation because the isolated gene does or does not have that mutation. Pet. App. 278a-79a. If the "isolated" gene in the lab differed from the gene in the body, Myriad could not reach that conclusion. Pet. App. 224a. And classic experiments established that when isolated DNA is reinserted into the cell, it functions as it did previously. 1J.A. 650-53.

Isolation does separate the gene from other parts of the body to which it is normally attached. The gene in the body is normally surrounded by and sometimes attached to other things, including proteins, that are collectively called chromatin. Pet. App. 262a; 1J.A. 644-46, 685-86. But the gene sequence, the information it includes, and the laws it embodies are the same whether in or out of the body.

Pet. App. 262a, 336a; 1J.A. 644-46. Even if separation from the chromatin were considered to create a structural difference, DNA is separated from the chromatin in the body during several naturally-occurring processes; the gene separated from the chromatin can be found in the body. Pet. App. 264a.

Isolation also separates the chromosome into fragments, breaking the bonds that link the pieces of the chromosome itself. Once again, the gene sequence, the information it includes, and the laws it embodies are the same whether the gene is in the body or contained in fragments made during the isolation process. But even if cutting the chromosome into pieces were considered to constitute a structural change, gene fragments exist in the body. These fragments result from naturally-occurring processes that break the bonds that hold the full chromosome together.[2] Those fragments are

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[2] Nature breaks the bonds that hold together the full chromosome (1) every time gametes are produced during the normal process of meiotic recombination; (2) during the cellular process by which cells make copies of themselves; (3) when DNA experiences a double strand break (which then is often repaired). *See* Wolf-Dietrich Heyer et al., *Holliday Junctions in the Eukaryotic Nucleus: Resolution in Sight?*, 28 Trends in Biochemical Sci. 548 (2003); *see also* Robyn L. Maher et al., *Coordination of DNA Replication and Recombination Activities in the Maintenance of Genomic Stability*, 112 J. of Cellular Biochemistry 2672 (2011).

The entire fetal and maternal genome can also be found in short fragments with broken covalent bonds in maternal plasma, and DNA can also be found in the blood of those suffering from cancer. Y.M. Dennis Lo et al., *Maternal Plasma DNA Sequencing Reveals the Genome-Wide Genetic and Mutational Profile of the Fetus*, 2 Sci. Translational Med. 61ra91 at 1 (2010); Maurice Stroun et al., *Isolation and* identical to the fragments created by Myriad when it isolates the gene.[3]

c. *The Patents*

Petitioners challenge nine patent claims on human genes. None of the challenged claims is limited to any particular use of the genes, any form of recombinant DNA, or a therapy (including a drug) involving the genes. None is limited to a method of looking at the gene. All of the claims are to the genes themselves and reach all structures and uses of the gene.

The key claims are claim 1 of Patent '282 and claim 1 of Patent '492. Those claims reach any "isolated DNA" that will create the proteins

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Characterization of DNA from the Plasma of Cancer Patients, 23 Eur. J. Cancer & Clinical Oncology 707 (1987).

[3] In the process of isolating a gene, DNA is fragmented and covalent bonds are broken. The scientist, however, does not decide or control the size or composition of the fragments; they are of random length and composition. Indeed, if a scientist were to isolate a gene of a person on Monday, and then do so again on Tuesday, it is likely the fragments would have a different size and composition. Many fragments are likely to include a portion of the BRCA1 or BRCA2 gene and a portion of the adjacent DNA. Bruce Alberts et al., *Molecular Biology of the Cell* Ch. 8 (4th ed. 2002); Robert L. Nussbaum et al., *Thompson and Thompson Genetics in Medicine* Ch. 4 (7th ed. 2007); Harvey Lodish et al., *Molecular Cell Biology* Ch. 7-8 (4th ed. 2000).

In addition, scientists sequencing genes after isolation generally do not chemically stitch the fragments back together to form longer segments, such as an entire gene. *See* 1J.A. 690-91. Sequencing generally relies on computers to recreate the gene sequence without creating a molecule or chemical that is an entire gene. *Id.*

naturally created by the BRCA1 and BRCA2 genes. More specifically, Patent '282, claim 1 reaches the BRCA1 gene:

> An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID No. 2.

Pet. App. 426a. SEQ ID No. 2 refers to a lengthy sequence of amino acids set forth in the patent. Patent '492, claim 1 is virtually identical, reaching the BRCA2 gene.

> An isolated DNA molecule coding for a BRCA2 polypeptide, said DNA molecule comprising a nucleic acid sequence encoding the amino acid sequence set forth in SEQ. ID. No. 2.

Pet. App. 427a.

All of the remaining claims use alternate terms to define the same genes or duplicatively claim alternate forms of the genes.

All nine claims use the same definitions of the two key terms: "isolated" and "DNA." "Isolated" is defined as: "An 'isolated' ... nucleic acid (*e.g.* an RNA, DNA, or a mixed polymer) is one which is substantially separated from other cellular components which naturally accompany a native human sequence or protein . . ." Patent '282, 19:8-12, 2J.A. 755. This definition of "isolated" comports with the ordinary understanding of the term in the field and there is no dispute between the parties over the meaning of the term.

"DNA" is defined broadly. The claims reach "all forms of mutations" (Patent '282, 12:31-32, 2J.A. 751) and "all allelic [nucleotide] variations" (Patent '282, 19:35-40, 2J.A. 755). They reach any DNA if it is as little as 60% similar to the specified DNA (Patent '282, 24:19, 2J.A. 757) and any DNA that creates proteins as little as 30% similar to the specified proteins (Patent '282, 24:62-63, 2J.A. 757). They reach all fragments of both the DNA and the proteins. *See* Patent '282, 6:26-28, 2J.A. 748 ("comprising all, or a portion of the BRCA1 locus or of a mutated BRCA1 locus, preferably at least 8 bases"); Patent '282, 19:1-5, 2J.A. 755 (reaches DNA that "can ... produce ... the polypeptide or a fragment thereof"); Patent '282, 19:41-43, 2J.A. 755 (reaches DNA that produces "fragment, homolog, or variant" of proteins); Patent '282, 20:34-35, 2J.A.755 (fragments as short as 15 nucleotides); Patent '282, 20:63-65, 2J.A. 755 (fragments as short as 8 nucleotides); Patent '282, 25:33-35, 2J.A. 758 (fragments as short as 5 amino acids). In 1998, Myriad wrote to one of the plaintiffs, Dr. Kazazian, and said specifically that the patents covered "any fragments of the BRCA1 gene." 1J.A. 168-69.

The claims also reach other forms of genetic material. They include "RNA, cDNA, genomic DNA, synthetic forms . . . ." Patent '282, 19:51-53, 2J.A. 755.[4] They reach DNA with or without "all coding sequences, all intervening sequences and regulatory elements." Patent '282, 19:35-40, 2J.A. 755. They reach DNA modified by "methylation" or other naturally-occurring biochemical or chemical modifications or not so modified. Patent '282, 19:53-55, 2J.A. 755; *see also* Pet. App. 263a.

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[4] cDNA, or complementary DNA, is discussed in Section II, *infra*. In short, it is DNA without the non-coding regions (regions seemingly unnecessary in creating the protein/polypeptide).

The key claims (Patent '282, claim 1 and Patent '492, claim 1) define the genes by the function given to the genes by nature and are not limited to any particular molecular structure or any particular use. Pet. App. 426a-27a. Because nature dictates that numerous DNA sequences can result in those polypeptides (proteins), 1J.A. 685-86, these claims unquestionably reach all uses of multiple compositions created by nature and defined by laws of nature, whether or not Myriad or anyone else has identified those compositions.

Claim 2 of Patent '282 defines the exact same gene by referring to a sequence of nucleotides that in nature represents one version of the BRCA1 gene. It reads:

> The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID No. 1.

Pet. App. 426a. This sequence reference is to a nucleotide sequence listed in the patent. Because the patents define the term "DNA" used in this claim identically to claim 1 to include all versions of the nucleotide sequence (and more), the sequence referenced is solely illustrative.

Indeed, if the claim reached only the specific sequence identified in the table, it would be confounding to geneticists who would not know if they infringed (*i.e.*, found that identical sequence) until they infringed (sequenced the gene). The claim would also be useless to Myriad. It is unlikely that more than a few people possess that exact sequence. If the specified sequence were the only sequence covered, it would not reach any sequence with any variants, mutations, or alterations. There is nothing in the patents to suggest that variants including non-coding regions are excluded from the definition of DNA.

The remaining claims are alternate descriptions, duplicative of the key claims, though three are of extraordinary breadth. Claim 6 of Patent '492 reaches any isolated BRCA2 DNA with a mutation that is "associated with a susceptibility to cancer." It reads:

> An isolated DNA molecule coding for a mutated form of the BRCA2 polypeptide set forth in SEQ ID No. 2, wherein said mutated form of the BRCA2 polypeptide is associated with a susceptibility to cancer.

Pet. App. 427a. The claim reaches any BRCA2 gene with harmful mutations regardless of whether another geneticist is the one who finds the mutation and identifies it as associated with any type of cancer. Indeed, for another geneticist to look for and find such a mutation would be infringing.

Claims 5 and 6 of patent '282 reach any segment of the BRCA1 DNA as short as 15 nucleotides. Claim 5 reaches any segment as short as 15 nucleotides that will create the proteins or any portion of the protein. Pet. App. 426a. Claim 6 reaches any 15 nucleotides of the BRCA1 gene. *Id.* More specifically, the claims read:

> 5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.
>
> 6. An isolated DNA having at least 15 nucleotides of the DNA of claim 2.

Because the claims reach DNA having "at least" 15 nucleotides, they reach longer sequences as well, including the entire gene. They also reach other genes. Because DNA is composed solely of the four nucleotides, there is extensive repetition in the genome. And, because the BRCA1 gene is large, it includes a huge number of 15 nucleotide sequences. Fifteen (15) nucleotide sequences from the BRCA1 gene can be found in virtually every other gene in the body. 1J.A. 631-34, 662-72. Moreover, as Judge Bryson indicated, claim 6 reaches nucleotide sequences in the non-coding regions as well as the coding regions throughout the genome. Pet. App. 114a.

The other claims, claim 1 of patent '473, claim 7 of patent '282, and claim 7 of patent '492, reach more specific, identified mutations. Pet. App. 426a, 428a. For example, claim 7 of '282 reads:

> An isolated DNA selected from the group consisting of: (a) a DNA having the nucleotide sequence set forth in SEQ ID No. 1 having T at nucleotide position 4056 . . .

These claims represent nothing more than Myriad describing a gene that contains some of the mutations caused by nature that nature has caused to be significant. Any geneticist must infringe (isolate the gene with the mutation) before she can determine that she has infringed (look to see if the composition includes the specified mutation). As with all the claims, they are not limited to any particular use.

d. *Proceedings Below*

This lawsuit began in 2009 with the filing of a complaint in the United States District Court for the Southern District of New York against the PTO, as well as the patent holders, Myriad Genetics and the directors of the University of Utah Research Foundation.[5] Plaintiffs included four national organizations of physicians, geneticists, researchers, clinicians, and other health professionals with a combined total of over 150,000 members, as well as six of the nation's leading geneticists, two genetic counselors, two women's health and breast cancer organizations, and six individual women who have been diagnosed with or are at risk of hereditary breast or ovarian cancer. Pet. App. 240a-48a.

Plaintiffs alleged in their complaint that the patent claims are invalid under Section 101 of the Patent Act because they cover products and laws of nature and abstract ideas. They also alleged that the effect of the challenged patent claims is to preempt scientific inquiry and medical care to the detriment of patients' health and scientific advancement, in violation of the First Amendment and Article I of the U.S. Constitution.

The complaint challenged fifteen claims from seven different patents. Pet. App. 297a-303a. Nine of the challenged claims from three patents cover the BRCA1 or BRCA2 genes.[6]

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[5] The University of Utah Research Foundation is an owner or co-owner of each of the patents containing the challenged claims, Pet. App. 248a, and has acted jointly with Myriad throughout the litigation.

Defendants moved to dismiss in the district court largely on the grounds that plaintiffs lacked standing. Pet. App. 361a. The court denied that motion. Pet. App. 412a. Both plaintiffs and Myriad subsequently moved for summary judgment, and the PTO moved for judgment on the pleadings. Pet. App. 237a. The district court granted plaintiffs' motion for summary judgment and denied Myriad's motion. *Id.* The constitutional claims against the PTO were dismissed based on the doctrine of constitutional avoidance. *Id.* at 357a.

The district court's 153-page, comprehensive opinion, Pet. App. 232a-357a, began by discussing the standard set by this Court for determining if a patented composition of matter – like the "isolated" DNA at issue here – has been sufficiently changed so that it is no longer a law or product of nature. Pet. App. 320a-23a (citing *Diamond v. Chakrabarty*, 447 U.S. 303 (1980); *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948); and *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1 (1931)).

The district court considered Myriad's arguments regarding both structural and functional differences between "isolated" DNA and the DNA inside the human body, ultimately concluding that none caused "isolated" genes to be "markedly different," *Chakrabarty*, 447 U.S. at 310, from genes in the body. Pet. App. 333a-44a. In holding that patents on isolated DNA claim laws and products of nature, the district court emphasized that the functionality of genes is based on their unique status as the embodiment of the information the body uses.

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[6] The complaint also challenged some method claims, none of which is now before the Court.

> [T]he information encoded by DNA reflects its primary biological function: directing the synthesis of *other* molecules in the body – namely, proteins, "biological molecules of enormous importance" which "catalyze biochemical reactions" and constitute the "major structural materials of the animal body."

Pet. App. 335a. The district court found that in isolating a gene, Myriad did not "alter its essential characteristic – its nucleotide sequence that is defined by nature and central to both its biological function within the cell and its utility as a research tool in the lab." Pet. App. 342a. To the extent any claims reached cDNA, the court also invalidated those claims for largely the same reason. Pet. App. 339a.

Myriad appealed to the Federal Circuit. Plaintiffs did not appeal the dismissal of the PTO, although plaintiffs continued to raise their First Amendment claims against the University of Utah defendants. The United States did, however, participate in the proceedings on the initial appeal and remand as *amicus curiae*, largely supporting plaintiffs.

A divided panel of the Federal Circuit reversed. The panel first dismissed all but one of the plaintiffs on the grounds that unless they had been personally threatened by Myriad, they did not have standing. Pet. App. 32a-42a. Each panel member wrote a separate opinion discussing the patentability of human genes. Judge Lourie held that in analyzing whether an "isolated" gene has "markedly different characteristics" from what is found in nature, the functionality of the gene is irrelevant. Pet. App. 55a. He held that "isolated" DNA is structurally different from DNA on the sole basis that in the process of removing DNA from the rest of the chromosome to which it is attached, a covalent bond is broken. Pet. App. 51a-57a.

Judge Moore, by contrast, found that both structure and function were relevant in determining if a composition is "markedly different" from what is found in nature. Pet. App. 85a. She found that a full-length "isolated" gene "does not clearly have a new utility and appears to simply serve the same ends devised by nature." Pet. App. 85a-86a. She wrote: "If I were deciding this case on a blank canvas, I might conclude that an isolated DNA sequence that includes most or all of a gene is not patentable subject matter." Pet. App. 86a. She nevertheless found full-length genes to be patentable because of the PTO's practice of granting gene patents and industry reliance on that practice. *Id.* She also opined that small fragments of the gene would be patentable because they could be used as probes or primers, while recognizing that none of the patents claims is limited to small fragments.[7] *See* Pet. App. 82a.

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[7] Probes and primers are pieces of DNA that are used in laboratories as part of the process of identifying or making

In his dissenting opinion, Judge Bryson held that the genes were not patentable. Pet. App. 102a. He reasoned:

> The structural differences between the claimed "isolated" genes and the corresponding portion of the native genes are irrelevant to the claim limitations, to the functioning of the genes, and to their utility in their isolated form. The use to which the genetic material can be put, *i.e.*, determining its sequence in a clinical setting is not a new use; it is only a consequence of possession. In order to sequence an isolated gene, each gene must function in the same manner in the laboratory as it does in the human body.

Pet. App. 110a.

Plaintiffs sought reconsideration by the panel on the grounds that the majority had introduced facts not in the record and that those facts were wrong. Specifically, plaintiffs noted that fragments of DNA with broken covalent bonds are created both in the body and in the "isolation" process; therefore, the breaking of a covalent bond did not distinguish "isolated" DNA from DNA in the body. Pls.-Appellees' Pet. for Panel Reh'g 4, *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 653

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copies of DNA. Pet. App. 264a-65a, 340a-41a. None of the challenged patent claims is limited to use as probes or primers.

F.3d 1329 (Fed. Cir. 2011); *see* 1J.A. 688-89. Rehearing was denied without opinion.[8]

This Court granted plaintiffs' petition for certiorari, vacated and remanded for further proceedings in light of *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012). Upon remand, each panel member adhered to his or her previous views.

Judge Lourie's consideration of *Mayo* was limited to two short paragraphs, which purported to distinguish *Mayo* on the ground that its reference to the preemptive effect of the invalidated patent in that case was applicable only to "laws of nature," not "products of nature." Rejecting the findings of the district court that DNA is a unique composition in its embodiment of natural laws, Judge Lourie ruled that the patents in this case do not claim a law of nature. Pet. App. 56a.

Judge Moore, unlike Judge Lourie, thought that *Mayo* "clearly ought to apply equally to manifestations of nature (composition claims)." Pet. App. 79a. Even so, she did not alter her conclusion or analysis in any material way to reflect *Mayo*'s holdings. Neither she nor Judge Lourie even referred to this Court's apparent rejection of her "reliance" argument in *Mayo*. 132 S. Ct. at 1305.

Judge Bryson's dissenting opinion applied this Court's reasoning in *Mayo*. "Has the applicant made an 'inventive' contribution to the product of nature? Does the claimed invention involve more than 'well-understood, routine, conventional' elements. Here, the answer to those questions is no." Pet. App. 112a. He also rejected the majority's deference to prior PTO practice, noting that it "give[s] the PTO lawmaking authority that Congress has not accorded it." Pet. App. 119a.

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[8] Myriad also filed a petition for panel rehearing, arguing that plaintiff Harry Ostrer lacked standing. The petition was denied without opinion. 1J.A. 19. Myriad raised the standing issue again following the *Mayo* remand, and the Federal Circuit rejected the argument in its second opinion. Pet. App. 25a n.6.

All three judges held that cDNA was patentable subject matter, *e.g.*, Pet. App. 47a-48a, 80a-81a, 98a, ignoring the district court's findings that none of the claims is limited to cDNA, that cDNA results from natural phenomena, and that cDNA sequences are found in the human genome. Pet. App. 268a, 339a. None of the Circuit judges addressed the claim to DNA with cancer-associated mutations or the other four claims that reach other mutations. None of the Circuit judges addressed Petitioners' constitutional claims.

Petitioners again sought review by this Court and the petition was granted, limited to Question 1: "Are human genes patentable?"

SUMMARY OF ARGUMENT

Myriad's patents on BRCA1 and BRCA2 violate long-established precedent that prohibits the patenting of laws and products of nature. *Chakrabarty*, 447 U.S. at 309. The Court's seminal Section 101 cases describe three different ways to evaluate patents to determine whether they impermissibly claim natural phenomena: whether the patented composition has markedly different characteristics from any found in nature, *id.* at 310; whether the patent is based on an inventive concept, *Mayo*, 132 S. Ct. at 1294; and whether the patent preempts use of the underlying product or law of nature, foreclosing future innovation out of proportion with the patentee's contribution, *id.* at 1301-03. When these three standards are applied to Myriad's claims, it is clear that the patents on isolated DNA must be found invalid.

First, isolated DNA does not have markedly different characteristics from any found in nature. Isolated DNA is simply removed from its natural environment; its structure and function remain the same. It also embodies the same genetic information – a law of nature – as in the body. The difference in structure discussed by the Federal Circuit majority opinion is based on a scientific misunderstanding, but even if correct, isolated DNA still could not be considered "markedly different" from the DNA in the body.

Second, patents on isolated DNA are not based on any inventive concept. Isolation was a routine, conventional activity at the time these patents were obtained. The only addition to the progress of science disclosed by these claims is the law of nature itself: that this DNA encodes for the BRCA1 or BRCA2 gene or protein. As in *Funk Brothers*, Myriad's discovery is simply of nature's handiwork. *See* 333 U.S. at 131.

Third, patenting isolated DNA ties up all basic uses of the BRCA1 and BRCA2 genes, foreclosing more future innovation than the underlying discovery could reasonably justify. *See Mayo*, 132 S. Ct. at 1301. Because isolation is required for any serious study, examination, or clinical or commercial use of the genes, these patents preempt all such activity. The patents exclude using the genes for research, clinical genetic testing, and the development of therapies. And these fears are not hypothetical; in practice, Myriad has used its patents to shut down clinical care and impede research.

The Court need not reach the question of whether cDNA, or complementary DNA, is patentable. Myriad has never argued that any of its claims are limited to cDNA, nor could it given the definitions in the patents. Even if some claims were so limited, cDNA's structure is dictated by nature and created by natural processes. Its function is likewise dictated by nature. It is neither inventive nor markedly different from DNA, and patenting it preempts use of a basic scientific and technological tool.

Patent-eligibility cannot be satisfied by the PTO's policy of issuing patents on isolated DNA and the industry reliance on such patents. This Court has never deferred to the PTO's Section 101 determinations, especially where, as here, they violate this Court's own precedent. Moreover, in *Mayo*, the Court rejected the same arguments about industry reliance made by Prometheus and Myriad, as amicus.

Finally, these patents run afoul of the First Amendment because they lock up the body of knowledge about these two genes. Myriad (and specifically in this context, the University of Utah) has the right to exclude all others from examining these genes in any context. Such restrictions on an entire field of knowledge give control over thought and pure information, in violation of the Constitution.

ARGUMENT

I. "ISOLATED DNA" IS NOT PATENTABLE SUBJECT MATTER UNDER SECTION 101.

The patenting of isolated DNA violates long-established precedent that prohibits the patenting of laws of nature, natural phenomena, products of nature, and abstract ideas. *Chakrabarty*, 447 U.S. at 309; *see also J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 134 (2001) ("'the relevant distinction' for purposes of § 101 is . . . 'between products of nature, whether living or not, and human-made inventions'"). "[T]hese exceptions have defined the reach of the statute as a matter of statutory *stare decisis* going back 150 years." *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010) (citing *Le Roy v. Tatham*, 55 U.S. 156, 174-75 (1853)). "Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." *Mayo*, 132 S. Ct. at 1293 (quoting *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)). This Court has explained repeatedly that "[s]uch discoveries are 'manifestations of . . . nature, free to all men and reserved exclusively to none.'" *Chakrabarty*, 447 U.S. at 309 (quoting *Funk Bros.*, 333 U.S. at 130). Otherwise, "there is a danger that the grant of patents that tie up their use will inhibit future innovation premised upon them." *Mayo*, 132 S. Ct. at 1301; *see also Funk Bros.*, 333 U.S. at 130-31.

Laws of nature, products of nature, and abstract ideas are not patentable based "on the more fundamental understanding that they are not the kind of 'discoveries' the statute was enacted to protect." *Parker v. Flook*, 437 U.S. 584, 593 (1978). A product of nature does not become a patentable invention based on utility, novelty, hard work, or the need to recoup investment. *See Mayo*, 132 S. Ct. at 1304. Nor can clever draftsmanship – such as adding the word "isolated" – rescue a claim that otherwise falls short of Section 101 scrutiny. The Court's "cases warn us against interpreting patent statutes in ways that make patent eligibility 'depend simply on the draftsman's art' without reference to the 'principles underlying the prohibition against patents for [natural laws].'" *Id.* at 1294 (quoting *Flook*, 437 U.S. at 593).

The central question in this case is whether "isolated DNA" is an unpatentable product or law of nature or a patentable invention. In *Mayo*, *Chakrabarty*, *Funk Brothers*, and *American Fruit Growers*, this Court has identified at least three different ways of distinguishing a product or law of nature from a patentable invention: whether the composition has any markedly different characteristics from any found in nature; whether the patent is based on an inventive concept; and whether the patent ties up use of the underlying natural phenomena. The three ways do not appear to be independent tests but ways of approaching the central question that must be applied on a case-by-case basis. When each is applied to the patent claims challenged in this case, the claims must be held invalid. Isolated DNA does not have markedly different characteristics from any found in nature, it is not based on an inventive concept, and patenting it preempts a huge number of valuable applications, far more than the underlying discovery can justify.

A. Isolated DNA Does Not Have Markedly Different Characteristics From Any Found In Nature.

In *Diamond v. Chakrabarty*, the last case in which this Court considered whether a composition of matter was patentable subject matter under Section 101, the Court held that a patent-eligible composition must have "a distinctive name, character [and] use" and "markedly different characteristics from any found in nature." *Chakrabarty*, 447 U.S. at 309-10 (alteration in original) (citation omitted). These criteria are consistent with the Court's statements in earlier Section 101 cases, including *Funk Brothers* and *American Fruit Growers*, and should guide the patent-eligibility determination here. Isolated DNA does not meet this standard.

Chakrabarty involved patents on bacteria that had been genetically-engineered to contain two or more plasmids, each capable of breaking down a component of crude oil, thus allowing the bacteria to degrade oil. *Id.* at 305. In concluding that the *Chakrabarty* bacterium was not a product of nature, the Court did not simply ask whether the bacterium was naturally-occurring, as had the Patent Office Board of Appeals below. *Id.* at 306 n.3. Instead, the Court delved deeper, examining the key characteristics of the claimed composition, including structure and function, to determine whether it was the work of nature.

Comparing the unpatentable combination of bacteria in *Funk Brothers* with the genetically-engineered and patentable *Chakrabarty* bacterium, the Court in *Chakrabarty* concluded that the latter has "markedly different characteristics from any found in nature," while the former's discovery is "nature's handiwork." *Id.* at 310. The *Chakrabarty* bacterium was both structurally and functionally different from the bacterium in its natural state, containing new genetic material and becoming capable of degrading oil in its new form. By contrast, the challenged patent in *Funk Brothers* was based on a naturally-occurring phenomenon; namely, the ability of certain "isolated" bacteria to efficiently fix nitrogen without inhibiting each other. Even though the bacteria did not exist together naturally and even though their aggregate nitrogen-fixing capability had been newly identified and had commercial utility, the Court invalidated the patent because the patent holder did "not create [a] state of inhibition or of non-inhibition in the bacteria." 333 U.S. at 130. The *Funk Brothers* bacteria did not have markedly different characteristics because their qualities were the work of nature, not of the patentee. *Funk Brothers* and *Chakrabarty* teach that the conditions of section 101 cannot be satisfied when compositions function as they would naturally, even when human ingenuity led to their packaging in a more useful form.

These cases drew on principles laid out in *American Fruit Growers*, in which the Court also grappled with the change necessary to create a patentable invention. The Court rejected the patenting of a fruit that had been treated with mold-resistant borax, even though the "complete article is not found in nature" and despite its "treatment, labor and manipulation." 283 U.S. at 11-12. The Court said: "There is no change in the name, appearance, or general character of the fruit. It remains a fresh orange fit only for the same beneficial uses as theretofore." *Id.* at 12. Even though the treated fruit had enhanced functionality because it would not rot as quickly, the primary use of the fruit remained the same – for human consumption – and thus the chemical treatment did not give it a "distinctive name, character or use." *Id.*

Under this precedent, the patents on isolated DNA improperly claim products and laws of nature. Isolated DNA does not have markedly different characteristics from DNA in the body – either in structure or function. Only because isolated DNA is not markedly different can Myriad tell patients if they face an increased risk of breast or ovarian cancer after performing diagnostic testing.

The claims' definition of the patented DNA based on biological characteristics, and the sheer number of molecules that are accordingly patented, provide key evidence that the claims reach products and laws of nature. The patents define the claim terms so broadly that they include the BRCA1 and BRCA2 genes of every person. They reach "all forms of mutations" or variations. Patent '282, 12:31-32, 2J.A. 751. They reach any DNA if it is as little as 60% similar to the specified DNA and any DNA that creates proteins as little as 30% similar to the specified proteins. Patent '282, 24:19, 2J.A. 757; Patent '282, 24:60-64, 2J.A. 757. They reach all fragments of both the DNA and the proteins. The claims also reach other forms of genetic material, including "RNA, cDNA, genomic DNA, synthetic forms..." Patent '282, 19:51-53, 2J.A. 755. They reach DNA with or without "all coding sequences, all intervening sequences and regulatory elements." Patent '282, 19:35-40; 2J.A. 755. They reach DNA modified by "methylation" or other biochemical or chemical modifications or not so modified. Patent '282, 19:56-67, 2J.A. 755; *see also* Pet. App. 263a. Thus while Myriad asserts that it has patented "a composition," it has actually patented hundreds of millions of compositions, most of which have as yet unidentified structures and functions, and all of which have been created by nature.

Even without resort to the patents' definitions of the claim terms, the claim language itself reaches a huge number of compositions, based on their naturally-occurring characteristics. Claim 1 of Patent '282 covers DNA that codes for all versions of the specified BRCA1 protein. The claim does not specify a particular gene that Myriad created or identified, but instead reaches any form of the gene that exists in nature. Claim 6 of Patent '492 reaches any isolated DNA coding for a mutated form of the BRCA2 polypeptide associated with susceptibility to cancer. The claim does not specify any of the mutations that are covered by the claim, nor the type of cancer that might be associated with a mutated form. Claims 5 and 6 of Patent '282 claim DNA sequences with as few as 15 nucleotide bases; small DNA segments sharing 15 nucleotide bases of the BRCA1 gene appear throughout the human genome. 1J.A. 631-34, 661-68. The claims do not seek to claim one or more specific genes (or even gene fragments) intentionally created and made different by the inventor, but instead claim every one of the segments that occur in nature.

Three of the four lower court judges correctly found that the structure of an isolated full-length gene is not markedly different from DNA in the body. Pet. App. 85a-86a, 102a-13a, 333a-44a. They rejected Myriad's argument that separating a gene from other parts of the body with which it is bound makes it structurally different. In so holding, they implicitly or explicitly acknowledged that Myriad's argument improperly confuses chromatin, the proteins and other elements attached to DNA in a cell, with the DNA itself. *See* 85a-86a, 108a, 337a-38a.

Judge Lourie found the structure was markedly different when a chromosome was split into constituent pieces such as genes. Pet. App. 51a-52a. As noted, he was simply wrong that fragments of chromosomes, with broken covalent bonds, do not appear in the body. *See infra*, p.10-11 n. 2. He was simply wrong in his implicit view that scientists isolating genes choose where to break covalent bonds. *See infra*, p. 11 n.3. But even were he correct, the idea that a piece of nature is patentable by breaking it into its constituent parts is fundamentally erroneous. Hydrogen separated from the oxygen to which it is bound in water is still a product of nature.

Likewise, removing DNA from its natural environment does not automatically create "markedly different characteristics." Many natural products must be physically separated from their natural environments in order to be used by mankind, but under *Funk Brothers*, that is not sufficient to render them patentable. The strains of bacteria in *Funk Brothers* were "isolated," removed from their natural environment, and aggregated so as to more efficiently fix nitrogen without inhibiting each other. 333 U.S. at 129-30. Nevertheless, they could not be patented. *Id.* at 132.

Judge Lourie focused narrowly on minor chemical changes incidental to isolation and viewed DNA's functional characteristics as irrelevant even though DNA's function is inherent in the claims. Pet. App. 55a. ("We recognize that biologists may think of molecules in terms of their uses, but genes are in fact materials having a chemical nature and, as such, are best described in patents by their structures rather than by their functions.") DNA is foremost an informational molecule, embodying the genetic code. Pet. App. 259a-60a, 334a-43a; 1J.A. 58-59, 130-33, 135-136, 232, 234-35, 561-62, 649-50, 680-81. "Today the idea that DNA carries genetic information in its long chain of nucleotides is so fundamental to biological thought that it is sometimes difficult to realize the enormous intellectual gap that it filled." Bruce Alberts et al., *Molecular Biology of the Cell* 98 (3d ed. 1994) (also noting "DNA is relatively inert chemically," *id.* at 104). Other chemicals in the human body remain the same, albeit in different quantities, from person to person. For example, H_2O, HOH and OH_2 all describe and represent the exact same water molecule; the nucleotide sequences of TAA, ATA and AAT encode entirely different amino acids. 1J.A. 676. Accordingly, the patents describe DNA by its nucleotide sequence, not the sugars and phosphates that make up its backbone, or the covalent bonds in between. 1J.A. 661-73, 676. There is no reading of the patent claims, case law, or science that justifies privileging the breaking of covalent bonds over all else (including other types of bonds and any analysis of function) in making patent eligibility determinations.

Turning to an analysis of functional differences between isolated genes and unisolated ones, Myriad has argued that genes are patentable because they can be used outside the body in ways they cannot be used inside the body. This argument not only ignores the breadth of the challenged claims, which are not limited to any such new uses, but it also fundamentally misunderstands the product of nature doctrine. Gold does not become patentable once taken out of a stream because it can be used in jewelry; kidneys do not become patentable once taken out of a body because they can be transplanted. Put another way, one potential use unspecified by the patent claim does not justify a patent on the product of nature itself and all uses of it. *See Mayo*, 132 S. Ct. at 1293-94.

None of the nine claims challenged is limited to a particular use or function.[9] Indeed, the two key claims themselves define "isolated DNA" according to a naturally-occurring function – namely, "coding for" a naturally-occurring polypeptide. *See, e.g.*, Pet. App. 426a (Claim 1 of Patent '282). Because this blueprint is the essential characteristic of DNA and remains the same before and after isolation, "isolated" DNA does not have markedly different characteristics from any found in nature, nor a distinctive name, character, or use. Both are DNA, the protein coded for by each is the same, and their use in storing and transmitting information about a person's heredity is identical. Indeed, classic experiments demonstrated that isolated DNA, once introduced into other cells and incorporated into chromosomes, would perform the very same function as it did while in the body. 1J.A. 650-53. The isolated DNA molecules "serve the ends nature originally provided and act quite independently of any effort of the patentee." *Funk Bros.*, 333 U.S. at 131. As the district court held, "DNA, and in particular the ordering of its nucleotides, therefore serves as the physical embodiment of laws of nature – those that define the construction of the human body." Pet. App. 335a. Only because this most basic function of DNA is not changed by isolation can Myriad perform its diagnostic tests and tell patients if they are at an increased risk of breast or ovarian cancer.

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[9] While claims 5 and 6 of '282 reach very short gene fragments, they reach full-length genes as well; both include DNA of *at least* 15 nucleotides. Thus, the discussion by Judge Moore analyzing the uses of gene fragments as primers and probes, App. at 82a-83a, must be rejected as dicta. None of the claims is limited to gene fragments, and none is limited to uses as primers and probes. *See infra*, pp. 11-17. And as a majority of the Federal Circuit and the district court held, scientists cannot use full-length genes as primers because they are too long. Pet. App. 85a, 115a; 1J.A. 673-74. Similarly, full-length genes cannot be used as probes unless altered by a process called fluorescence. Pet. App. 85a; 1J.A. 672-74; *see also* 1J.A. 656, 693.

B. The Challenged Claims Are Not Based On Any Inventive Concept But Instead Claim Products And Laws Of Nature.

In *Mayo*, the Court highlighted another method of determining patent-eligibility found in its precedent – whether the patent is based on an "inventive concept." 132 S. Ct. at 1294, 1297. *Mayo* asked, does the claim arise from an "'inventive concept,' sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself"? *Id.* at 1294. Does it "add enough" or "simply append[] conventional steps, specified at a high level of generality, to laws of nature [or] natural phenomena"? *Id.* at 1300.

Mayo and *Funk Brothers* elaborate on the inventive concept analysis. In *Mayo*, the Court found that the claims were not inventive, despite transformations that occurred during the administration of a drug and determination of metabolite levels, because nothing of significance was added to the law of nature – the patient's response to a drug. The steps of administering a drug and determining metabolite levels were routine, conventional science. *Id.* at 1297-98. The only addition in the patent claim was the identification by Prometheus of the metabolite levels that indicate drug efficacy. *Id.* at 1297. The claims simply "inform a relevant audience about certain laws of nature." *Id.* at 1298. In *Funk Brothers*, even though the patentee arguably advanced the field because his combination of bacteria "contributed utility and economy to the manufacture and distribution of commercial inoculants," 333 U.S. at 130-31, the Court found that Section 101 was not satisfied. The only addition by the patentee was the discovery of the natural qualities of the bacteria: "[T]here is no invention here unless the discovery that certain strains of the several species of these bacteria are non-inhibitive and may thus be safely mixed is invention. But we cannot so hold without allowing a patent to issue on one of the ancient secrets of nature now disclosed." *Id.* at 132.

Myriad identified the naturally-existing gene, which embodies the natural law that some naturally-occurring mutations of that gene increase a woman's risk of breast and ovarian cancer. Myriad isolated those genes, but isolation of DNA was a well-known technique at the time these patents were sought, and continues to be a routine, conventional preparatory step for using human genes in research and clinical practice. 1J.A. 642-43, 689. The only addition of the "isolated" DNA claims to the progress of science is disclosure of a natural genetic sequence created by a natural law itself – the fact that this sequence of DNA encodes for the BRCA protein and embodies information important for understanding a person's heredity and disease susceptibility. The claimed composition is a discovery of nature's handiwork. *Chakrabarty*, 447 U.S. at 310. And while isolation is needed to use the sequence to identify the law of nature in a particular person's gene, the genetic sequence "itself exists in principle apart from any human action." *Mayo*, 132 S. Ct. at 1297. Just as administering a drug triggered manifestation of a person's natural metabolism of thiopurine in *Mayo*, isolating DNA merely makes visible a person's inherited genetic makeup.

Perhaps the most obvious illustration of the lack of an "inventive" concept in Myriad's claims is claim 6 of Patent '492. It reaches any isolated BRCA2 DNA that is "associated with a susceptibility to cancer." Pet. App. 427a. Myriad has identified a gene in the body, but now claims any mutations created by nature that are found by anyone at any time and are "associated with a susceptibility to cancer." Myriad surely cannot claim to have invented mutations identified by others.

In some ways, the inventive concept analysis overlaps with the "markedly different characteristics from any found in nature" standard discussed *supra*, particularly when compositions of matter are at issue. The focus on inventive concept is helpful, however, in explaining the difference between novelty and utility inquiries and the Section 101 exceptions, which lower courts sometimes have blurred. The inventive concept required to satisfy Section 101 depends on determining whether what the inventor has "added" to the field is a product or law of nature, or whether the inventor has transformed it into more. Although it is possible that the novelty or utility criteria would be satisfied by the new discovery of a natural phenomenon or a discovery of its utility, Section 101 *per se* precludes such patents. *See Mayo*, 132 S. Ct. at 1303-04. *See also In re Marden*, 47 F.2d 958, 959 (C.C.P.A. 1931) (rejecting patent on pure vanadium, because "pure vanadium is not new in the inventive sense, and, it being a product of nature, no one is entitled to a monopoly of the same").

Other cases apply the inventive concept analysis and offer further support for the invalidity of these claims. The Third Circuit held that a patent applicant named Coolidge could not patent "[s]ubstantially pure tungsten having ductility and high tensile strength," despite the superiority of purified tungsten over its naturally-occurring, brittle form. *Gen. Elec. Co. v. De Forest Radio Co.*, 28 F.2d 641, 643 (3d Cir. 1928).

> Naturally we inquire who created pure tungsten. Coolidge? No. It existed in nature and doubtless has existed there

> for centuries. The fact that no one before Coolidge found it there does not negative its origin or existence.

Id. at 643. *General Electric* confirms that courts must examine whether the composition and any characteristics specified in the claims were invented by the patentee or were the work of nature. *See also In re Marden*, 47 F.2d 957 (C.C.P.A. 1931) (rejecting patent on purified uranium); *In re Marden*, 47 F.2d at 958 (rejecting patent on purified vanadium); *In re Merz*, 97 F.2d 599 (C.C.P.A. 1936) (rejecting patent on purified ultramarine). In the early case of *Ex Parte Latimer*, the Patent Commissioner rejected a patent on fibers extracted from pine needles that could more easily be spun and woven. 1889 Dec. Comm'r Pat. 123 (1889). The applicant did not invent the length, strength, or fineness of the fibers: "[n]ature made them so and not the process by which they are taken from the leaf or the needle." *Id.* at 125. *Cf. Am. Wood Paper Co. v. Fibre Disintegrating Co.*, 90 U.S. 566, 593-94 (1874) (finding that cellulose derived from wood and useful for making paper was unpatentable).

Myriad did not invent the isolated DNA. Myriad did not invent any of the characteristics of DNA that are incidental to its isolation. Myriad did not invent the length, composition, or function of the BRCA1 or BRCA2 genes; human biology determined these qualities of the two genes. Pet. App. 106a-07a, 339a, 342a-44a.

C. The Challenged Claims Preempt Uses Of Products And Laws Of Nature.

As *Mayo* reaffirmed, a key aspect of the product or law of nature analysis turns on whether the patent preempts use of the laws and products of nature. Does the patent "risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries"? 132 S. Ct. at 1294. Patents on natural phenomena present roadblocks to scientific inquiry and innovation, thus running counter to the constitutional mandate that patents "promote the progress of science." U.S. Const. art. I § 8, cl. 8; *Chakrabarty*, 447 U.S. at 315. "[M]onopolization of [basic scientific and technological] tools through the grant of a patent might tend to impede innovation rather than it would tend to promote it." *Mayo*, 132 S. Ct. at 1293. Thus, the Court's precedents "warn us against upholding patents that claim processes that too broadly preempt the use of a natural law." *Id.* at 1294; *see also Bilski*, 130 S. Ct. at 3231 ("Allowing petitioners to patent risk hedging would pre-empt use of this approach in all fields, and would effectively grant a monopoly over an abstract idea."); *Funk Bros.*, 333 U.S. at 130 ("The qualities of these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men. . . . He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes."); *O'Reilly v. Morse*, 56 U.S. 62, 113 (1853) (The patentee's claim on any machinery or process using electric current to mark characters at a distance "shuts the door against inventions of other persons . .

. ."). The preemption inquiry under Section 101 is determined by whether the patent claim authorizes the patentee to foreclose use of a product or law of nature. *Bilski*, 130 S. Ct. at 3230.

Claims on isolated DNA impermissibly preempt scientific and medical work, far beyond what Myriad's contribution can justify.[10] *See Mayo*, 132 S. Ct. at 1301. The challenged claims cover all isolated forms of the naturally-occurring genes, whether previously identified or not. Some, like claim 6 of '492, expressly claim additional laws of nature (mutations that correlate with an increased risk of cancer), whether previously identified or not. All of the claims reach all uses of the genes in DNA, cDNA, or RNA form and all variants and fragments of the genes, including future uses not yet identified or technically achievable. And because isolation is a necessary step in any serious study, research, or clinical or commercial use of the native DNA, the patents raise the same concerns about patenting a "building-block" that has previously troubled the Court. *See id.* at 1303. They also undermine the patent system by giving Myriad the right to any applications of isolated DNA without disclosing them or even having done the work to develop them. *See*

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[10] While Myriad's work should be credited, it is important to recognize that Myriad built upon the contributions of others. The process of isolation has been performed since as early as 1869. Pet. App. 255a n.3 (citing Ralf Dahm, *Discovering DNA: Friedrich Miescher and the Early Years of Nucleic Acid Research*, 122 Hum. Genetics 565 (2008)). Other scientists discovered the locus of the BRCA1 gene years before Myriad sequenced it, and the federal government poured millions of dollars of funding into the search for the gene. Pet. App. 272a-78a; 1J.A. 247-52.

Morse, 56 U.S. at 113 ("And if he can secure the exclusive use by his present patent he may vary it with every new discovery and development of the science, and need place no description of the new manner, process, or machinery, upon the records of the patent office . . . he claims an exclusive right to use a manner and process which he has not described and indeed had not invented, and therefore could not describe when he obtained his patent."). These patents thus tie up all basic uses of the genes, "foreclose[ing] more future innovation than the underlying discovery could reasonably justify." *Mayo*, 132 S. Ct. at 1292.

Because the patent claims reach all uses of the two human genes, Myriad has the authority to prevent all study of them. When patent exclusivity extends to genes, science is seriously undermined.

> From the point of view of scientific research, human genetic sequences are as basic as you can get in terms of biological information. They are as basic as the elements in the periodic table. Patenting a gene or genetic sequence impedes scientific progress much the same way that patenting a naturally occurring element such as oxygen or gold would impede science.

1J.A. 136 (statement of Nobel Prize-winning biologist John Sulston); *see also* Rep. of the Sec'y's Advisory Comm. on Genetics, Health, and Soc'y, *Gene Patents and Licensing Practices and their Impact on Patient Access to Genetic Tests* 90 (Apr. 2010) (hereinafter "SACGHS Report") (US gene patent law "not only threatens medical progress, it may also drive valuable genetic research" to other countries); Francis S. Collins, *The Language of Life: DNA and the Revolution in Personalized Medicine* 113 (2010) ("The information contained in our shared instruction book is so fundamental, and requires so much further research to understand its utility, that patenting it at the earliest stage is like putting up a whole lot of unnecessary toll booths on the road to discovery."). Nobel Prize-winning economist Joseph Stiglitz stated that gene patents held by Myriad and others "did not contribute to the store of knowledge, but they impeded innovation in several ways." 1J.A. 708-09.

The effect of the patents has been to prevent and deter research. Pet. App. 290a-92a; 1J.A. 144, 257-58, 623-24, 708-10, 714-18. The contested claims have inhibited others' willingness to engage in research. Over half of all labs surveyed as part of a government-funded study reported "deciding not to develop a new clinical genetic test because of a gene patent or license." 1J.A. 144. Another study found that 46% of surveyed geneticists felt that gene patents had "delayed or limited their research." *Id.* Some geneticists have felt a deep discomfort with conducting research on the BRCA genes because Myriad has prohibited them from disclosing genetic information to research subjects and sharply limited what it considers to be research. 1J.A. 59-60; Kimberly Blanton, *Corporate Takeover Exploiting the U.S. Patent System*, Boston Globe Mag., Feb. 24, 2002, at 10. And scholars looking closely at gene patents found they had "persistent negative effects on subsequent scientific research." Heidi L. Williams, *Intellectual Property Rights and Innovation: Evidence from the Human Genome* ii

(Nat'l Bureau of Econ. Research, Working Paper No. 16213, 2010). *See also* 1J.A. 708-09 ("The Myriad and similar patents ... impeded innovation in several ways...more significant perhaps is the impediment to follow-up research...[and] even for basic research..."); 1J.A. 717-18; SACGHS Report at 63-65; Sam Kean, *The Human Genome (Patent) Project*, 331 Sci. 530 (Feb. 4, 2011) (describing high barriers faced by biotechnology companies, including patents that are impossible to circumvent and the millions of dollars required to investigate relevant patent claims and to attempt to negotiate licensing deals).

These patents bar access to people's genetic information. In *Mayo*, the Court suggested that a claim on a new drug would not raise the concern that invalidated Prometheus' patents because another company could develop another drug treating the same condition without infringing. *Mayo*, 132 S. Ct. at 1302-03. In contrast, the "isolated" DNA claims are claims that do preempt future use of laws and products of nature because another entity cannot invent a gene that embodies a person's BRCA1 and BRCA2 genetic information. 1J.A. 135-36. The claims that specifically claim DNA with as few as 15 nucleotide bases preempt scientific work to an even greater extent, because sequences sharing at least 15 nucleotides of the BRCA1 gene appear throughout the genome. Pet. App. 226a-27a; 1J.A. 631-35, 663-72.

These patents preclude using the DNA for the development of drugs, instruments, and treatment methods. Although the BRCA genetic testing Myriad offers is a useful application of isolated DNA, this value is dwarfed by the potential applications of isolated DNA in new therapeutics, biomedical devices and instruments, and sequencing technologies. *See* Jonathan D. Rockoff & Jess Bravin, *Gene Patents Face Reckoning*, Wall St. J., Dec. 30, 2012 (describing companies, even those which control gene patents, that believe ending gene patents could be a "positive development . . . because it would open new opportunities to develop new testing services based on gene discoveries."). Some of these new applications might relate to breast and ovarian cancer, and some might not[11]; yet, they all are precluded by the patents if they require using the BRCA DNA. Myriad has used the challenged claims to prevent clinical testing of these genes by any other lab, even when others could do so at lower cost, to confirm results, or to ensure testing quality. Many women, upon obtaining results from Myriad, wish to get a second opinion before they make life-changing medical decisions, such as obtaining or refraining from prophylactic surgery. Women cannot obtain confirmatory testing through other labs except for one small set of mutations. Pet. App. 288a-89a; SACGHS Report at 33-34. Myriad also prevents others from providing testing at a lower price, or for free, and only 130 million of America's 308 million people currently receive insurance coverage for their testing. 1J.A. 536.

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[11] The BRCA genes have been linked to other cancers, including prostate and pancreatic. *See, e.g.*, Srinath Sundararajan et al., *The Relevance of BRCA Genetics to Prostate Cancer Pathogenesis and Treatment*, 9 Clinical Advances in Hematology & Oncology 748 (2011); Kathleen M. Murphy et al., *Evaluation of Candidate Genes MAP2K4, MADH4, ACVR1B and BRCA2 in Familial Pancreatic Cancer: Deleterious BRCA2 Mutations in 17%*, 62 Cancer Res. 3789 (2002).

These claims give rise to the same concern expressed by this Court in *Mayo* regarding how patents "threaten to inhibit the development of more refined treatment recommendations." *Mayo*, 132 S. Ct. at 1302. The "isolated" DNA claims allow Myriad to dictate the standard of testing that is offered. It is undisputed that for several years, Myriad was performing tests that did not identify all known mutations. Women with mutations not detected by Myriad's tests were and continue to be given falsely reassuring results. 1J.A. 61, 151, 210, 220-21, 258; Robert Langreth, *Myriad Stymies Cancer Answers by Impeding Data Sharing*, Bloomberg, Dec. 28, 2012. Indeed, Myriad continues to separate testing for large genetic rearrangements from its standard testing, even though national guidelines recommend that patients receive such testing. Nat'l Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian* HBOC-2, MS-14-15 (2012). Moreover, Myriad's monopoly on the BRCA genes prevents other laboratories from including these genes when clinically assaying the over twenty genes now known to be associated with hereditary risk for breast and ovarian cancer or when using next generation testing methods. *See, e.g.*, Tom Walsh et al., *Detection of Inherited Mutations for Breast and Ovarian Cancer Using Genomic Capture and Massively Parallel Sequencing*, Proc. Nat'l Acad. Sci. 3 (2010); Hilmi Ozcelik et al., *Long-Range PCR and Next-Generation Sequencing of BRCA1 and BRCA2 in Breast Cancer*, 14 J. Molecular Diagnostics 419, 467 (2012); SACGHS Report at 39-40; *see also* 1J.A. 59-60, 86-91, 208-11, 219-24, 623; Fed. Cir. App. A2813.

The patents also have interfered with deepening our knowledge about these genes. Scientists routinely share information about the importance of particular genes and particular gene mutations. 1J.A. 137-39. Because the patents have authorized Myriad to maintain a monopoly on clinical testing, they have permitted Myriad to control a huge amount of data on the nature and significance of variants in the BRCA1 and BRCA2 genes. For the last several years, Myriad has refused to share that data with the scientific community and has no obligation to collaborate with others. Pet. App. 289a-93a; 1J.A. 62, 91, 206-09; Andrew Pollack, *Despite Gene Patent Victory, Myriad Genetics Faces Challenges*, N.Y. Times, Aug. 24, 2011; *see also* 1J.A. 136-39. If additional labs could engage in testing, the scientific community would know considerably more, particularly about those alterations of the gene whose significance is not now known. 1J.A. 62, 113-14, 222-23. Through its patents, Myriad not only commands the law of nature that is embodied by the BRCA genes, but also the laws of nature relating to how the BRCA genes function in tandem with other genes and genetic factors and how the genes might be linked to diseases other than breast and ovarian cancer – key scientific insights required for the development of personalized medicine. 1J.A. 138-39.

Despite *Mayo*'s concerns about the impact of patents on innovation, the Federal Circuit majority refused to consider how the patents preempt use of laws and products of nature, impeding clinical and scientific work. Pet. App. 43a-44a, 58a-59a. The wide-ranging harmful impact of these patents has led the medical and scientific establishment, including the American Medical Association, the

American Society of Human Genetics, and patient advocacy groups, to oppose them.

Because virtually every conceivable scientific use of DNA requires that it be isolated, and because the patents do not specify a single BRCA molecule or a single use of the DNA but instead cover all of them, the patents give exclusivity over the BRCA1 and BRCA2 genes itself, and their preemptive effect mandates a finding of invalidity.

II. cDNA IS NOT PATENTABLE SUBJECT MATTER.

Although Myriad has *never* asserted that any of its claims are limited to cDNA, and Petitioners agree that none of the challenged claims is limited to cDNA, the Department of Justice (and Judges Lourie and Bryson of the Federal Circuit after remand) thought one or more claims were limited to cDNA. Pet. App. 47a n.9, 100a. The judges and DOJ apparently relied on the description of the sequence listed in the patent's table (Patent '282, 2J.A. 779) rather than the definition of DNA as used in the patent claim. Patent '282, 19:51-53, 2J.A. 755, 822.

This Court need not and should not reach the question of the patentability of cDNA. The challenged claims define "isolated DNA" to include a variety of types of compositions including genomic DNA (DNA with coding and non-coding regions) and cDNA (DNA with coding regions). *See, e.g.*, Patent '282, 19:14-18, 19:51-53, 2J.A. 755. Thus, if the definitions of DNA that Myriad insisted upon in its patents are credited, as they must be, a ruling finding isolated DNA unpatentable would defeat all of the challenged claims.

If, however, the Court interprets any of the challenged claims to be limited to just cDNA and chooses to address the patent-eligibility of cDNA, it should find that claims on cDNA impermissibly claim products and laws of nature.

At the simplest level, cDNA is identical to DNA except the non-coding regions have been removed. Myriad does not decide which nucleotides to remove. Nature dictates which are coding and which are not. Thus, comparing the capital letters listed in patent '282, FIG 10 (which is DNA with coding regions in capital letters and non-coding regions in small letters) with SEQ ID. NO.1 reveals that they are identical. 2J.A. 738-45. They are not "markedly different" in structure; only the parts nature has made seemingly unnecessary are removed. If DNA is analogized to a newspaper, cDNA is the identical newspaper without the ads.

cDNA and DNA also are not "markedly different" in function. Definitionally, they encode the same polypeptide/protein. BRCA1 or BRCA2 cDNA "codes for" or creates the BRCA1 or BRCA2 polypeptide.

Equally importantly, the non-coding regions are removed in the body by nature. In the process of making a protein, the DNA is first converted into mRNA by a naturally-occurring process. mRNA is fundamentally DNA but does not contain the non-coding regions.[12] Pet. App. 265a-67a. To go to cDNA, the mRNA is removed from the body and converted into cDNA by repeating the complementary binding process that nature has dictated to re-create the coding regions of the original DNA. Pet. App. 266a-69a. Thus, if the DNA sequence was a GCGTAT, the mRNA sequence will be CGCUTU, and the cDNA sequence will once again be GCGTAT as it was in the original DNA.[13]

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[12] It is admittedly more complicated. As noted above, DNA consists of four nucleotides: A, G, T, and C. Pet. App. 257a. Each uniquely binds to (or connects with) a binding partner. Thus, A always binds to T and C always binds to G. Pet. App. 258a; 1J.A. 234. When mRNA is made in the cell, the

There is no scientific or legal distinction between isolated genomic DNA and cDNA that warrants treating their patent eligibility differently. Their characters and functions are both dictated by nature, not the patentee, and therefore neither has "markedly different characteristics from any found in nature." The critical difference, exclusion of the non-coding regions, is accomplished entirely within the cell, by natural processes, without any human intervention. cDNA "is an exact copy of one of the protein coding sequences encoded by the original genomic DNA . . . In this respect, cDNA contains the identical protein coding informational content as the DNA in the body . ." Pet. App. 268a; *see also* Pet. App. 339a ("not only are the coding sequences contained in the claimed DNA identical to those

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nucleotide in the DNA is replaced by its binding partner. Pet. App. 15a, 266a. Thus, if the DNA nucleotides are GCG, the mRNA nucleotides made by the body will be a CGC. mRNA also utilizes a chemical called uracil (U), in place of DNA's T which binds to A. Pet. App. 15a, 266a. These changes are analogous to the simplest of all codes, in which the letter A is always replaced by B and B by C. The substance has not changed and the changes are made by the body. Finally, mRNA has different endings from DNA, called untranslated regions.

[13] Of course, the full cDNA sequence excludes the non-coding regions.

found in native DNA, the particular arrangement of those coding sequences is the result of the natural phenomena of RNA splicing.") As a result, cDNA simply does not have "markedly different characteristics from any found in nature."

Although cDNA is frequently created in the laboratory using the above-described process, scientists have documented the existence of the BRCA1 pseudogene1, a segment of the BRCA1 cDNA, in the human genome. Pet. App. 268a; 1J.A. 658-59, 674-75. A ruling that DNA is not patentable because it is a product of nature necessarily would require a ruling that pseudogenes (or cDNA) are not patentable for the same reason.

Even though cDNA is generally made in the laboratory, that fact alone does not render it patentable subject matter. The nucleotide sequence of cDNA is dictated by nature, not by the lab technician; indeed, the technician does not even know the sequence beforehand. And presumably, the fruit at issue in *American Fruit Growers* was not treated while still on the tree; nor were the *Funk* strains of bacteria isolated and combined in their natural habitat. *Chakrabarty* would not have presented a close question if the legal standard turned on whether the bacterium was created in the laboratory or in the wild. The setting for the creation of the patented composition does not determine its patent eligibility. Nor is the synthetic nature of the composition decisive. In *Cochrane v. Badische Anilin & Soda Fabrik*, the Court held that an artificial version of a natural red dye called alizarine that was produced by manipulating another compound through acid, heat, water, or distillation could not be patented. 111 U.S. 293, 311 (1884). Although the artificial version was brighter than observed in nature and prepared through a new, man-made process, it was unpatentable because of its similarity to the natural product. That it was synthesized, rather than naturally-occurring, did not make it a patentable composition of matter, though the process of synthesizing artificial alizarine could be patented. *Id.* Lastly, the fact that cDNA does not include non-protein-coding sequences found in DNA does not transform it into an invention. As the Court said in *American Fruit Growers*, "every change in an article is the result of treatment, labor, and manipulation," but the key question remains, is it no longer a product of nature? 283 U.S. at 12.

There is no inventive concept in cDNA. The process resulting in cDNA was known long before Myriad obtained its patents and is not before the Court. 1J.A. 675; Jeffrey Ross et al., *In Vitro Synthesis of DNA Complementary to Purified Rabbit Globin mRNA*, 69 Proc. Nat. Acad. Sci. USA 264 (1972). cDNA is a composition whose structure and function is dictated by and created by nature.

Lastly, patenting cDNA preempts use of a basic scientific tool that serves as the basis for many genetic discoveries. For example, many genetic engineering experiments involve producing and tinkering with cDNA. Any foreseeable innovations that apply genetic engineering techniques in developing new ways of repairing mutated genes would require utilizing cDNA. cDNA is also the basis for RNA sequencing that is used to quantify how a gene is functioning.[14] Furthermore, cDNA is modified and used in the development of recombinant drugs or therapeutic proteins. Finding ways to change cDNA to produce a more useful protein are true discoveries worthy of patent protection; the baseline cDNA is not.

Given cDNA's biological relationship to naturally-occurring mRNA, its existence in the naturally-occurring human genome, its creation based on the naturally-occurring biological machinery of the cell, and its status as a "basic scientific and technological tool," cDNA is not patentable subject matter.

III. THE COURT SHOULD DECIDE THE PATENTABILITY OF HUMAN GENES WITHOUT REGARD TO INDUSTRY RELIANCE ON PATENT OFFICE PRACTICE.

Judge Moore thought full-length genes were not patentable subject matter but provided the critical vote upholding the challenged claims because the PTO has long approved patents on genes and industry has relied upon them. The PTO's practice is largely irrelevant. Were it not, it would be unusual, not routine, for courts to invalidate patents. For example, roughly 37% of all patents challenged on obviousness grounds were held invalid. *See* Univ. of Houston Law Center Inst. for Intell. Prop. & Info.

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[14] RNA analysis is distinct from genetic sequencing in measuring a different type of gene malfunction. *See, e.g.*, Gina Kolata, *In Treatment for Leukemia, Glimpses of the Future*, N.Y. Times, July 8, 2012, at A1 (describing how researchers found the cause for one oncologist's leukemia using RNA sequencing).

Law, Full Calendar Year 2011 Report, http://www.patstats.org/2011_Full_Year_Report.html. Moreover, the U.S. government, in the course of this litigation, has filed two briefs arguing that isolated DNA is not patentable.

That the PTO's practice is based on written guidelines is equally irrelevant. The 2001 PTO Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001) are guidelines for patent examiners, not binding on this Court. *See Hill-Rom Co., Inc. v. Kinetic Concepts, Inc.*, 209 F.3d 1337, 1341 n.* (Fed. Cir. 2000). They are also remarkably free of any analysis of their rationale, simply stating that "isolated" genes do not exist in the body. Not only is this incorrect, but it misapprehends this Court's analysis for distinguishing products or laws of nature from inventions.

Perhaps more troubling is Judge Moore's view that patentees attain "adverse possession" on products or laws of nature, Pet. App. 119a, if industry has relied on them. Presumably, industry relies on any issued patent. But more importantly, this Court confronted and flatly rejected this argument in *Mayo*. 132 S. Ct. at 1304-05 (referring to the industry reliance argument of Prometheus and "several amici"); Brief for Myriad Genetics, Inc., as Amicus Curiae Supporting Respondent, *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012) (No. 10-1150), 2011 WL 5373694.

It is not for the Court to balance policy considerations and dole out special patent protection for DNA. The Court stated that such special protection must be expressly required by Congress: "And we must recognize the role of Congress in crafting more finely tailored rules where necessary. We need not determine here whether, from a policy perspective, increased protection for discoveries of diagnostic laws of nature is desirable." *Mayo*, 132 S. Ct. at 1305 (citations omitted). The *Bilski* concurrence, approving the invalidation of a business method patent, similarly noted that Congress, not the Court, should select the policy that best serves the constitutional aim, "[a]nd absent a discernible signal from Congress, we proceed cautiously when dealing with patents that press on the limits of the 'standard written into the constitution.'" 130 S. Ct. at 3253 (citation omitted); *see also Microsoft Corp. v. AT&T Corp.* 550 U.S. 437, 458 (2007) ("[O]ur precedent leads us to leave in Congress' court the patent-protective determination AT&T seeks."); *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1998) (finding exemption from infringement where statute was ambiguous as to scope of exemption).

It is not clear that Congress could constitutionally abolish the product or law of nature doctrine in whole or in part, but it has not done so with respect to human genes. This Court should apply long-standing doctrine without regard to PTO deference and industry reliance and find the challenged claims unpatentable.

IV. PATENT CLAIMS ON ISOLATED DNA ALSO VIOLATE THE FIRST AMENDMENT BECAUSE THEY AMOUNT TO A GRANT OF EXCLUSIVE CONTROL OVER A BODY OF KNOWLEDGE.

The First Amendment limits the reach of intellectual property laws. In copyright, where the potential conflict is more obvious, this Court has suggested that doctrines, like the idea/expression distinction, that are incorporated into statute are required by the First Amendment. *Harper & Row Publishers, Inc. v. Nation Enters.*, 471 U.S. 539, 556 (1985); *Eldred v. Ashcroft*, 537 U.S. 186, 219 (2003). *See also Salinger v. Colting*, 641 F. Supp. 2d 250, 255 (S.D.N.Y. 2009), *rev'd on other grounds*, 607 F.3d 68 (2d Cir. 2010); *Maxtone-Graham v. Burtchaell*, 631 F. Supp. 1432, 1435 (S.D.N.Y. 1986). Although the section 101 doctrine prohibiting patenting of natural phenomena has not been described previously as compelled by the First Amendment, there can be little doubt that granting patents that give control over an entire body of knowledge would violate the First Amendment. Indeed, the Court's concern about tying up basic scientific and technological tools highlights the priority placed on preventing patents that impede scientific thought and innovation. *Mayo*, 132 S. Ct. at 1293; *see also* Gary L. Francione, *Experimentation and the Marketplace Theory of the First Amendment*, 136 U. Pa. L. Rev. 417, 428 (1987).

For a typical invention, such as a carburetor, others can examine how the new carburetor functions once the patent is published and develop a better carburetor using different materials or methods. By contrast, if "isolated" oxygen were patented, no one could invent a new oxygen, and no one could study how it reacts in numerous scientific contexts without the patentee's permission. Similarly, once a human gene is patented, nobody can invent a new human gene, and nobody can access that particular human genetic information.[15] *See* 1J.A. 63, 139. Because patent claims on the isolated BRCA1 and BRCA2 DNA prevent access to each person's genetic information, and accordingly deprive scientists of the opportunity to examine and study the genes, they are fundamentally different from patents on carburetors.

Indeed, rather than leading to a greater understanding or a better product, the patent claims challenged in this case exclude others from further work with naturally-occurring genes. *E.g.*, 1J.A. 139, 148, 152. Myriad has used its exclusive authority to amass an enormous amount of information critical to the health of every American. Myriad refuses to allow others to obtain the information themselves or to share the information with the medical and scientific communities. The claims thus give entire control over a body of knowledge and over pure information to Myriad. That, under the First Amendment, is impermissible. *See Ashcroft v. Free Speech Coal.*, 535 U.S. 234, 253 (2002) ("First Amendment freedoms are most in danger when the government seeks to control thought or to justify its laws for that impermissible end. The right to think is the beginning of freedom . . . ."); *see also* John A. Robertson, *The Scientist's Right to Research: A Constitutional Analysis*, 51 S. Cal. L. Rev. 1203, 1217-18 (1977) (concluding that "[i]f the first amendment serves to protect free trade in the dissemination of ideas and information, it must also protect the necessary preconditions of speech, such as the production of ideas and information through research.").

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[15] Genes with new sequences can be invented, of course, that have never existed in nature. Those are not at issue here.

The serious constitutional violation raised by these patent claims provides an additional reason for the Court to construe the statute to find the claims invalid. The district court found it unnecessary to reach the constitutional questions, invoking the doctrine of constitutional avoidance. Pet. App. 357a. However, if the Court finds the claims valid under the statute, it should find them unconstitutional under the First Amendment.

CONCLUSION

For the foregoing reasons, the patent claims should be held invalid.

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RESPONDENT'S BRIEF

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,

Petitioners.

v.

MYRIAD GENETICS, INC., ET AL.,

Respondents.

On Writ Of Certiorari
To The United States Court Of Appeals
For The Federal Circuit

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QUESTION PRESENTED

The claimed isolated molecules of deoxyribonucleic acid are particular molecular compositions designed based on the Myriad inventors' identification and characterization of the structure of the BRCA genes, and separated from other cellular content by the inventors based on those designs. These molecules are used to detect and analyze mutations in human tissue, which aid in determining a patient's genetic predisposition risk to breast and ovarian cancers.

The question presented is:

Did the Federal Circuit correctly apply 35 U.S.C. § 101 to conclude that these particular molecules are "product[s] of human ingenuity 'having a distinctive name, character [and] use,'" particularly where the general legal rule followed by courts for 30 years has been to allow such patent claims, where the U.S. Patent and Trademark Office ("USPTO") has issued similar patents since at least 1982 and confirmed in the 2001 *Utility Guidelines* that such isolated molecules are patent-eligible as human-made inventions under § 101, where investors and technology companies have placed significant reliance in these settled property rights over the last 30 years, where the alternative dividing line is indefensible under law or science, and where the challenged claims do not preempt or preclude the use of alternative technologies to identify a patient's cancer predisposition?

LIST OF PARTIES

Petitioners' brief correctly lists the parties to the Federal Circuit proceedings. *See* Pet. Br. i-ii. However, the Federal Circuit held that only one plaintiff, Dr. Harry Ostrer, had standing. Pet. App. 41a. Because this Court declined petitioners' certiorari request to review whether the remaining plaintiffs also had standing in this case, *see Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 694 (2012), Ostrer is the sole petitioner before this Court.

CORPORATE DISCLOSURE STATEMENT

No parent or publicly held company owns 10% or more of the stock of respondent Myriad Genetics, Inc. or of the University of Utah Research Foundation.

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JURISDICTION

Petitioners' jurisdictional statement omits that Myriad has always contested any live case or controversy between Myriad and Dr. Harry Ostrer, the only remaining petitioner. There is still no case or controversy. *See* pp. 17-22, *infra*.

STATEMENT

1. In passing the 1952 Patent Act, and in particular 35 U.S.C. § 101, "Congress intended statutory subject matter to 'include anything under the sun that is made by man.'" *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) (quoting S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952); H. R. Rep. No. 1923, 82d Cong., 2d Sess., 6 (1952)). "Made by man" means, for composition-of-matter claims, that they are "a product of human ingenuity." *Id.*

"[M]anifestations of . . . nature," such as a new plant found in the wild or the qualities of a naturally-occurring bacterium, *see Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948), are of course not "product[s] of human ingenuity," because they occur without aid of human faculties. But because "[e]verything that happens may be deemed 'the work of nature,' and any patentable composite exemplifies in its properties 'the laws of nature,'" *id.* at 134-35 (Frankfurter, J., concurring), it is important to define clearly the line between an unpatentable manifestation of nature and a patent-eligible composition. As this Court has held, the answer to that inquiry depends on whether the composition—even if created with naturally-occurring starting materials, and even if resembling or performing some of the same functions as something found in nature—was the result of "human ingenuity," *i.e.*, "invention."

Chakrabarty, 447 U.S. at 309; *see Mackay Radio & Tel. Co. v. Radio Corp. of Am.*, 306 U.S. 86, 94 (1939).

No one would doubt the patent-eligibility of a newly-created chemical composition that, when applied in a laboratory to a person's blood or tissue sample, could detect a mutation genetically predisposing her to a risk of breast or ovarian cancer, thereby allowing her to take proactive measures to prolong her life even before cancer actually strikes. That is what Myriad's patented molecules are—and they were never available to the world until Myriad's scientists applied their inventive faculties to a previously undistinguished mass of genetic matter in order to identify, define, and create the isolated DNA molecules.

2. It has long been established that specific isolated molecules of deoxyribonucleic acid ("DNA") are patent-eligible. "Isolated" means that a human being has defined the molecule and separated it from the complex of genetic material that accompanies it in the body, or (as with complementary DNA, or cDNA) synthetically created the molecule in a laboratory. Such molecules may include recombinant, cloned, or synthesized DNA isolates. Pet. App. 19a-20a. This human design and action transforms the molecule's physical structure and alters its chemistry. JA413-19.

Two years after *Chakrabarty*, the USPTO granted the first human DNA-related patents. *See* Eric J. Rogers, *Can You Patent Genes? Yes and No*, 93 J. PAT. & TRADEMARK OFF. SOC'Y 19, 19 & n.3 (2010) (citing patents issued March 30 and December 14, 1982). Over the next 30-plus years, the USPTO and the courts reinforced the rule of patent-eligibility for isolated DNA molecules, recognizing that creating a particular novel isolated molecule represents a patentable advancement over what existed in nature. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991). The USPTO has granted over 40,000 patents drawn to genetic material, almost 3,000 of which are specifically directed to isolated DNA molecules. Indeed, the challenged Myriad patents began issuing 15 years ago (all will expire in the next two years). *See* Rogers, *supra*, at 19, 40; Pet. App. 61a-62a, 87a-88a; JA527-28.

In the mid-1990s, when DNA-related claims had been issuing for over a decade and upheld by the Federal Circuit, the USPTO evaluated its approach for compliance with § 101, and "to ensure that examination was of sufficiently high quality." JA519, 581. The USPTO held a public hearing, received comments, and in 1995 issued its initial guidelines for patent examiners. These guidelines concluded that "any 'non-naturally occurring manufacture or composition of matter'" is patent-eligible under § 101. *Utility Examination Guidelines*, 60 Fed. Reg. 36,263 (July 14, 1995); JA581-84.

In 2001, the USPTO again considered the rule that isolated molecules derived from genetic material can be patent-eligible. JA521-22. Following an extensive notice-and-comment process and further review of the statute and precedent, the USPTO promulgated another set of *Utility Guidelines*. 66 Fed. Reg. 1092 (Jan. 5, 2001). Under the USPTO's 2001 *Guidelines*, so long as "the [patent] application discloses a specific, substantial, and credible utility for the claimed isolated and purified gene, the isolated and purified gene composition may be patentable." *Id.* at 1093.[1] The USPTO elaborated that "[a] patent on a gene covers the isolated and purified gene but does not cover the gene as it occurs in nature." *Id.*; *see also* JA522 (declaration of John Doll, later Commissioner for Patents, explaining the reasoning underlying the 2001 *Guidelines*). When a patent claims isolated DNA molecules, the USPTO requires a symbolic recitation of the nucleotide or amino acid sequence in what is called a "SEQ ID." *See* 37 C.F.R. §§ 1.821-1.825; *Manual of Patent Examining Procedure* §§ 2420 *et seq.* ("MPEP").

The USPTO's *Guidelines* followed the long-established rule that isolates or extracts of natural products may be patented.[2] The USPTO, and, ultimately, the courts, had long considered extracts or isolates of natural products to be both patent-eligible *and* patentable. *See, e.g.*, *Kuehmstead v. Farbenfabriken of Elberfeld Co.*, 179 F. 701 (7th Cir. 1910) (aspirin); *In re Kratz*, 592 F.2d 1169 (C.C.P.A. 1979) (substantially pure 2-methyl-2-pentenoic acid (2M2PA)—the molecule that imparts strawberries' distinctive flavor and odor—mixed with an adjuvant); *In re Bergstrom*, 427 F.2d 1394 (C.C.P.A. 1970) (substantially pure PGE2 and PGE3 (prostaglandins)); *Merck Co. v. Olin Mathieson Chem. Corp.*, 253 F.2d 156 (4th Cir. 1958) (purified vitamin B12 obtained from extracts of streptomyces cultures); *Parke-Davis & Co. v. H.K. Mulford & Co.*, 196 F. 496 (2d Cir. 1912) (substantially pure adrenalin derived from cow glands).

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[1] Petitioners have never challenged the utility of Myriad's claimed molecules. *E.g.*, Pet. Br. 9.

[2] *See, e.g.*, U.S. Patent Nos. 644,077 (1900) (pure acetyl salicylic acid (aspirin)); 1,898,199 (1933) (isolated digitalis—a substance obtained from the foxglove plant for the treatment of heart conditions); 2,105,486 (1938) (whooping-cough vaccine derived from bacterial extracts); 2,698,843 (1955) (antimicrobial composition extracted and purified from a corn fungus); 3,929,992 (1975) (Rapamycin—an immunosuppressant produced by a soil bacterium and used to prevent rejection of transplanted organs); 3,983,140 (1976) (cholesterol-lowering compound purified from a Penicillium sp.); 5,135,864 (1992) (the HIV virus).

3. Countless companies and investors have risked billions of dollars to research and develop advances under this promise of stable patent protection. *See* Letter from Eric Y. Drogin & Robert A. Armitage to David J. Kappos re: Genetic Diagnostic Testing 5 (Apr. 16, 2012), *available at* www.uspto.gov/aia_implementation/gene-comment-aba.pdf. One was a small Utah start-up, Helix Technologies. In the mid-1990s, scientists at Helix, now known as Myriad Genetics, successfully identified, defined, and isolated the BRCA molecules, and disclosed their creation and utilities to the world. This momentous scientific advancement displayed Myriad's inventors' significant scientific skill, insight, and invention.

Genes in the body are chemically connected in unbroken strands of DNA wrapped around proteins to form chromosomes. By 1990, it had been hypothesized that at least one very large chromosomal location correlated with susceptibility to breast and ovarian cancers, but there was much confusion in the field at that time over any more particular location. JA479-80, 493, 499, 747. "Given the confusion, a skilled artisan would not have known in which chromosomal region to look for the *BRCA1* gene." JA480, 747.

Myriad succeeded where others failed by applying its genetic-mapping technology to define and locate the precise genetic regions associated with mutations predisposing a patient to breast and ovarian cancers. JA481-83, 484-87 (a collaborating scientist described this technique as "the closest thing to magic"). These regions came to be known as the "BRCA1 gene" and the "BRCA2 gene." JA498-501. This stage of the inventive process itself depended on an enormous amount of human judgment, including how to define the beginning and end of these genes. JA480-90, 495-99, 507-11.

Building on this foundation, Myriad then studied the BRCA genes to identify their particular structures, attributes, and characteristics. Once it deciphered this information, it sought to improve existing techniques for diagnosing an individual's hereditary cancer risk by designing isolated DNA molecules and producing them in the laboratory (by manufacturing or synthesis). JA481-90, 495-99, 506-11. These applications of human ingenuity yielded new, never-before-available molecules that can now be used to detect mutations associated with a risk of hereditary breast or ovarian cancer (the principal cancers associated with mutations in the BRCA1 and BRCA2 regions of the genome).

As the patents describe, the specific isolated BRCA1 and BRCA2 molecules, once defined, were either separated from surrounding genomic and cellular matter at precise locations chosen by the Myriad inventors, or assembled in a laboratory (in the case of cDNA). Pet. App. 14a; *e.g.*, JA748, 755. Their human inventive choices defined the particular isolated molecules, free from genetic and other surrounding material, to enable their utility outside the body in ways that naturally-occurring DNA in the body lacks. Pet. App. 18a; JA413-19, 468-69. To function within the body, a gene cannot be isolated, but must be physically bound to other genes, nucleic acids, and proteins within the chromosome.

Two critical uses of the claimed molecules are to "probe" for target DNA in a patient sample or to "prime" the production of copies of the target DNA in the laboratory. *E.g.*, 753, 756. When so used, these isolated molecules are designed to "zero-in" on and bind to (hybridize) the BRCA gene in the much larger genome in the human sample—akin to finding "a grain of sand" within the Empire State Building. JA436-37. This hybridization can only take place because of the natural "pairing" quality of the molecule's nucleotide bases (the bases denoted "A" and "T" bind with one another, as do the bases denoted "G" and "C"), *in combination with* the human ingenuity involved in designing those particular molecules. Probes and primers thus function because of the *differences* from native DNA brought about by the ingenuity of Myriad's inventors. JA135, 415-18.

473-75, 524-25, 564-65, 595-601, 603, 608-11.[3] DNA molecules in the body (native DNA), by contrast, cannot be used as probes or primers, because they are chemically bound up with other matter. *See generally* Bruce Alberts et al., MOLECULAR BIOLOGY OF THE CELL 98-99, 291-93, 296-98 (3d ed. 1994).

4. To recoup its vast investment in creating these new molecules, Myriad uses them as part of a molecular testing service for targeted isolation and sequencing of a patient's BRCA DNA. Myriad's BRAC*Analysis*® test, conducted on a patient's blood or oral-rinse sample, filled a long-felt need by drastically improving accuracy in determining

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[3] To be used as a "probe," an isolated molecule is typically "tagged" with a marker (*e.g.*, a radioactive or fluorescent compound) so that it can be detected once it binds (hybridizes) with the targeted area of the human sample. JA413-19, 473-75, 525, 595-96, 598-601, 610-11; Bruce Alberts et al., MOLECULAR BIOLOGY OF THE CELL 295-96 (3d ed. 1994).

As a "primer," the isolated DNA molecule is used in a reiterative process called a polymerase chain reaction ("PCR"). Like probes, primers are designed to bind to the target BRCA DNA in the human sample. In PCR, the primer is combined with, *inter alia*, the human sample and a heat-stable enzyme (that does not exist in the human body). The free reactive end of the bound primer serves as a starting point for PCR to synthesize a copy of the target DNA. The reaction is repeated to "amplify"—exponentially duplicate—DNA copies of the target. JA413-19, 473-75, 353, 432, 597. The resulting high concentration of the DNA copies allows scientists to better analyze and ascertain the sequence of the target DNA in the patient's sample to detect a genetic mutation. JA353; Alberts, *supra*, at 316-17.

patients' predisposition to hereditary breast and ovarian cancers. JA341, 350-51, 356-57. Myriad also spent hundreds of millions of dollars over the past 20 years educating patients, doctors, medical associations, and insurers (including Medicare and Medicaid) about genetic testing, and it provides free testing for patients in need. JA344-47, 535-37. Moreover, Myriad has dedicated staff to help patients navigate the complexities of insurance coverage and reduce their out-of-pocket expenses, so that over 90% of BRAC*Analysis*® tests are covered by insurance at over 90% of the cost, with those patients paying less than $100 on average. JA344, 348. Today, because of Myriad's inventions and its investments—secured by the promise of a limited period of patent protection—high-quality BRCA testing, widely approved by doctors and insurers, has been conducted on over one million patients.[4] JA346-49, 351-55.

Those of ordinary skill could not have created Myriad's patented molecules in the mid-1990s. One of Myriad's principal competitors followed conventional wisdom by cloning large pieces of human DNA, rather than Myriad's counterintuitive approach of using smaller pieces, which required many more clones and was thought at the time to be a "mistake." JA484-86. The competitor's large clones, however, "had a deletion at the site of the BRCA1 gene," so their research would never have succeeded in defining the molecule now known as BRCA1 to permit further study for isolation. JA485. Their leader eventually acknowledged these flaws, described Myriad's identification of the BRCA1 gene "as 'beautiful' and 'lovely' and deserving of all the praise it might win," and named Myriad's approach "the winne[r] of the day." JA485, 501-02. A competitor with respect to BRCA2 similarly failed because one of its tools was missing critical aspects of the gene's structure. JA507.

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[4] Ostrer incorrectly implies that only 130 million Americans have access to BRAC*Analysis*®, Pet. Br. 45, but that counts only those with private insurance. The test is also covered under Medicare and Medicaid. JA347-48, 536.

Myriad disclosed its inventions to the public in a series of patents. Contrary to Ostrer's mischaracterizations of the patents' effects, Pet. Br. 7-9, 43-45, since the patents issued, over 18,000 researchers have conducted studies on BRCA1/2 genes, published over 8,000 papers, and conducted over 130 clinical trials. JA336-37, 455-56. Indeed, one named plaintiff conceded that she may "sequence the BRCA1 and BRCA2 genes for purely research purposes," and has been doing so without impediment. JA59-60. And multiple laboratories provide "second opinions" regarding BRAC*Analysis*® results. JA364-65.

5. Nine claims in three patents remain at issue. Claims 1, 2, 5, 6, and 7 of U.S. Patent No. 5,747,282 (the "'282 patent") and claim 1 of U.S. Patent No. 5,693,473 (the "'473 patent") relate to BRCA1. Claims 1, 6, and 7 of U.S. Patent No. 5,837,492 (the "'492 patent") relate to BRCA2.

Each of the nine claims expressly recites "[a]n isolated DNA" or "[a]n isolated DNA molecule." An "isolated" molecule is defined in the patents as a molecule "which is substantially separated from other cellular components which naturally accompany a native human sequence or protein, e.g., ribosomes, polymerases, many other human genome sequences and proteins. The term embraces a nucleic acid sequence or protein removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems." *E.g.*, JA755 (19:8-19). Some of the claims (claims 2, 6, and 7 of the '282 patent and claim 7 of the '492 patent) are drawn even more narrowly and cover only cDNA molecules—"synthetic molecules built by scientists" in a laboratory. U.S. Br. 4.

Claims to isolated DNA molecules. Claim 1 of the '282 patent is representative of these claims: "An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO: 2." JA822. SEQ ID NO:2 depicts the amino-acid sequence of the BRCA1 protein (the expression product of BRCA1 DNA). JA785-90. Claim 1 of the '492 patent is similar, but is directed to isolated BRCA2 DNA molecules. JA1028.

Claim 5 of the '282 patent is directed to portions of the isolated BRCA1 DNA molecules recited in claim 1: "An isolated DNA having at least 15 nucleotides of the DNA of claim 1." JA822.

Claim 6 of the '492 patent is directed to an "isolated DNA molecule" of the kind claimed in claim 1 of that patent, but having a mutation of the BRCA2 polypeptide "associated with susceptibility to cancer." JA1028.

Finally, claim 1 of the '473 patent is directed to specific, identified alterations of isolated BRCA1 DNA molecules. JA930.

Claims limited to cDNA molecules. The "isolated DNA" claims encompass cDNA molecules as well as other isolated molecules. A second group of claims, however, is limited to cDNA molecules. In addition to being "isolated," cDNA molecules differ from native DNA because, *inter alia*, they are synthesized in laboratories and exclude certain regulatory and other non-protein-coding sequences (introns) found in native DNA and include only protein-coding DNA (exons). JA779-85.

Claim 2 of the '282 patent is exemplary: "The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1." JA822. The "wherein" clause limits the claim to particular cDNA molecules—*i.e.*, the nucleotide sequence of just the coding regions, omitting introns, depicted in SEQ ID NO: 1. JA779 ("Molecule Type: cDNA"). Far from being "solely illustrative," Pet. Br. 14, the sequence in SEQ ID NO: 1 defines the structure of the claimed molecules by requiring that they have the recited cDNA sequence.

Claim 6 of the '282 patent is directed to limited portions of the molecules of claim 2: "An isolated DNA having at least 15 nucleotides of the DNA of claim 2." JA822.

The other two claims deal with cDNA molecules having genetic mutations. Claim 7 of the '282 patent is directed to specific, identified alterations of isolated BRCA1 cDNA molecules. JA822. Claim 7 of the '492 patent is directed to mutations of a BRCA2 cDNA composition. JA1028.

6. This declaratory-judgment action began when the American Civil Liberties Union Foundation ("ACLU") and the Public Patent Foundation ("PubPat") recruited 20 plaintiffs to, in ACLU counsel's words, "sue somebody." Joe Palazzolo, *Law Blog Fireside: Chris Hansen, the ACLU's Longest-Serving Attorney*, Wall Street Journal Law Blog (Nov. 9, 2012), http://blogs.wsj.com/law/2012/11/09/law-blog-fireside-chris-hansen-the-aclus-longest-serving-attorney (last visited Mar. 6, 2013) ("WSJ Law Blog"). The complaint alleged, *inter alia*, that a few selected claims of seven patents-in-suit are not patent-eligible under 35 U.S.C. § 101 and unconstitutional under Article I, § 8, cl. 8 of, and the First and Fourteenth Amendments to, the Constitution. JA54. In statutory terms, the entire lawsuit concerned only the narrow issue of § 101 patent-eligibility—there are no patentability challenges under §§ 102 (novelty), 103 (non-obviousness), or 112 (disclosure).

Myriad moved to dismiss for lack of a real and immediate case or controversy between Myriad and any of the plaintiffs. Pet. App. 25a. Although the district court sustained jurisdiction as to all plaintiffs, *id.* at 406a, the Court of Appeals subsequently held that only one, Ostrer, had a live controversy with Myriad, *id.* at 41a. In their certiorari petition, the other 19 plaintiffs unsuccessfully tried to obtain review of this ruling. Pet. i; JA21. Ostrer is thus the sole petitioner before the Court.

7. On summary judgment, after conducting only limited claim construction, the district court held all of the challenged claims patent-ineligible because

"none of the structural and functional differences cited by Myriad" constitute a marked difference between native DNA and the claimed isolated DNA molecules. Pet. App. 336a. (The district court declined to address plaintiffs' constitutional claims. *Id.* at 355a n.61.) The Federal Circuit reversed. *Id.* at 179a. After this Court decided ***Mayo Collaborative Services v. Prometheus Laboratories, Inc.***, 132 S. Ct. 1289 (2012), it granted plaintiffs' first certiorari petition, vacated the Federal Circuit's judgment, and remanded for further consideration in light of ***Mayo***, Pet. App. 1a.

On remand, the Federal Circuit reexamined the challenged claims to isolated DNA molecules in light of ***Mayo*** and again held them patent-eligible. Each member of the panel noted that the fundamental inquiry remained the ***Chakrabarty*** test understood in light of ***Mayo***, evaluating whether the compositions were the product of human ingenuity.

Judge Lourie's lead opinion focused on the variety of differences between the claimed compositions and native DNA caused by human intervention, *e.g.*, isolated DNA molecules are "free-standing," are "synthesized" or have "chemically severed" backbones, and have significantly fewer nucleotides than native DNA. *Id.* at 49a, 51a (internal quotations and brackets omitted). Concurring, Judge Moore further explained that these structural changes to these molecules imparted new utilities. *Id.* at 80a-86a. Both judges underscored that the patent-eligibility of these claims is confirmed by the decades-long practice of granting patents on isolated DNA molecules, and the investing and inventing communities' settled expectations based on that practice. *Id.* at 61a-62a, 87a-94a.

Dissenting in part, Judge Bryson agreed that cDNA claims are patent-eligible. *Id.* at 113a-14a; *accord* 47a, 54a, 80a-81a. For the other claims, he agreed that isolating DNA molecules causes a "material change made to those genes from their natural state," but he downplayed the significance of the change as "necessarily incidental to the extraction of the genes from the environment in which they are found." *Id.* at 102a.

SUMMARY OF ARGUMENT

I. The Federal Circuit distorted fundamental Article III principles to find that one of 20 declaratory-judgment plaintiffs, recruited by their counsel to bring this test case, presented a live case or controversy. A declaratory-judgment plaintiff must have a "real and substantial" dispute with the defendant, "of sufficient immediacy and reality to warrant the issuance of a declaratory judgment." *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118, 127 (2007) (internal quotations and citations omitted). This threat must exist "at the commencement of the litigation," *Davis v. FEC*, 554 U.S. 724, 732 (2008), and "subsis[t] through all stages" of proceedings thereafter, *Lewis v. Continental Bank Corp.*, 494 U.S. 472, 477-78 (1990).

Here, the alleged controversy was neither "real" nor "immediate," but manufactured and stale, when the complaint was filed in 2009. The Federal Circuit nonetheless concluded that Ostrer had a justiciable dispute with Myriad because he suspended BRCA testing in 1998 after NYU, his then-employer, received but did not accept a license offer from

Myriad. Even if that single communication had been sufficient to support jurisdiction in 1998, there were no further communications between Myriad, Ostrer, and NYU, and Ostrer's subjective conclusion that the 1998 license offer chilled his commercial activity when he filed suit in 2009 does not present a real or immediate dispute to support declaratory-judgment jurisdiction.

Further, Ostrer mooted any conceivable controversy when he left NYU in 2011 and moved to a different institution with *no* past history or communications with Myriad. In short, this is a lawyer-driven case with no concrete interest to support a declaratory-judgment action.

II. Were the Court to reach the merits, it should affirm. Section 101 broadly covers "anything under the sun that is made by man." *Chakrabarty*, 447 U.S. at 309. The claimed isolated DNA molecules are physical, chemical compositions squarely within the plain language of § 101. The claims also clearly fall on the inventive side of the line drawn by this Court's precedent and exemplified in the USPTO's *Guidelines*. With no intervening dissent from Congress, continuing this approach respects the longstanding rule that isolated DNA molecules such as those claimed here warrant patent-eligibility—a judgment on which industry, inventors, and investors alike have relied in researching, developing, and bringing new and useful medical products to the world. *See J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124 (1996).

Ostrer instead offers an ambiguous, three-part test that obscures the language of the statute and the "product of human ingenuity" principle established by precedent and long applied by the USPTO. He asks whether a "product of nature" has "markedly different" characteristics and improperly "preempts" research. These formulations possess neither the crispness nor the legal accuracy required to determine whether a composition is the product of human ingenuity. Ostrer further confuses the issue before the Court by misstating the claim language, the record, and scientific facts, and by conflating the conditions for ultimate patentability with the sole question presented concerning patent-eligibility. The claims, all compositions made by man, satisfy § 101. The judgment should be affirmed.

ARGUMENT

I. OSTRER HAD—AND NOW HAS—NO "REAL AND IMMEDIATE" DISPUTE WITH MYRIAD TO SUPPORT HIS DECLARATORY-JUDGMENT COMPLAINT

The Federal Circuit found that 19 plaintiffs had no real dispute with Myriad, but it strained to find a case or controversy as to one, Dr. Ostrer. The court's ruling was contrary to this Court's precedent and fundamental Article III principles that ensure resort to the federal courts only for real, live controversies. Ostrer had no real and immediate dispute with Myriad when this lawsuit was filed in 2009, and by his own unilateral conduct has none now.

A. Ostrer Never Had A "Real And Immediate" Dispute With Myriad

The Federal Circuit reasoned that Ostrer had presented a justiciable declaratory-judgment action because he averred that he "will immediately begin such [BRCA] testing" if Myriad's patents were invalidated. Pet. App. 35a-36a. The court distinguished Ostrer's averments from those of two other plaintiffs, Drs. Ganguly and Kazazian, who only said they would "consider" resuming testing in that event. *Id.*

The reality and immediacy of the claimed dispute should not have been evaluated in such a unilateral fashion. Myriad's contribution to the supposed controversy was a single 1998 communication to NYU's Molecular Genetics Laboratory, nominally addressed to Ostrer because he was the lab's director at the time. Pet. App. 33a-36a; JA94-110. NYU did not sign the proposed license agreement enclosed with Myriad's letter, and there was no further communication until Ostrer and his co-plaintiffs filed this action in 2009. JA110. Radio silence for eleven years.

Under no plausible definition of "immediate" can an eleven-year-old, never-responded-to licensing offer to an employer serve to establish an Article III case or controversy with an employee. The Federal Circuit disagreed, reasoning that "the relevant circumstances remain unchanged" since 1998, describing Ostrer as somehow "laboring under Myriad's threat of infringement liability" since receiving the license offer. Pet. App. 37a.

But it was Ostrer's unilateral decision to suspend genetic testing, based entirely on his speculations about what Myriad might have done had Ostrer continued testing, that caused his claimed injury. That is not enough. *See Clapper v. Amnesty Int'l USA*, No. 11-1025, 2013 WL 673253, at *10 (U.S. Feb. 26, 2013) (expressing the Court's "usual reluctance to endorse standing theories that rest on speculation about the decisions of independent actors"). In *Laird v. Tatum*, 408 U.S. 1, 2 (1972), this Court dismissed a declaratory-judgment action where plaintiffs alleged that the Army's "surveillance of lawful and peaceful civilian political activity" chilled their First Amendment speech rights. Plaintiffs' "[a]llegations of a subjective 'chill' [we]re not an adequate substitute for a claim of specific present objective harm or a threat of specific future harm." *Id.* at 13-14; *see also Clapper*, 2013 WL 673253, at *12. Just as the *Laird* plaintiffs' allegation that they spoke less in light of the surveillance program was inadequate, Ostrer cannot demonstrate standing by averring that, after serving as a conduit for Myriad's licensing offer to NYU, he ceased certain testing activities in 1998 (a fact he never communicated to Myriad), and continued that cessation on his own accord, again without any further communication from Myriad, until the 2009 complaint. Neither in *Laird*, nor in *Clapper*, nor here, was there a "certainly impending" injury traceable to Myriad. *Whitmore v. Arkansas*, 495 U.S. 149, 158 (1990); *Clapper*, 2013 WL 673253, at *7. The harm created by Ostrer's eleven-year-long cessation of testing is not a "real and immediate" bilateral dispute between parties, but unilateral, self-inflicted injury.

The filing of this suit in 2009 had nothing to do with Myriad or the existence of any real dispute, and everything to do with Ostrer's counsel's manufacturing of this cause. The ACLU's strategy was "let's sue somebody" (WSJ Law Blog, *supra*), and PubPat's stated intent was to "rend[er] invalid patents on many other genes . . . . We just had to pick one case as our case." C.A. App. 7387-88.

Neither "the intensity of [Ostrer's or his counsel's] interest [n]or the fervor of his advocacy" substitutes for the constitutional requirement of a real and immediate controversy. *Valley Forge Christian Coll. v. Ams. United for Separation of Church & State, Inc.*, 454 U.S. 464, 486 (1982). The eleven-year-old licensing offer to NYU—alone or in combination with Ostrer's unilateral cessation of testing—did not create a "real and immediate" controversy when this case was filed in 2009.

B. Even If Myriad's 1998 Licensing Offer To NYU Could Serve As A Basis For This Declaratory-Judgment Action, Ostrer's 2011 Departure From NYU Mooted This Case

If a controversy ceases to exist during any stage of a case, it is properly dismissed as moot. *Preiser v. Newkirk*, 422 U.S. 395, 401-03 (1975). On August 29, 2011, while this case was pending on appeal, Ostrer ended his employment at NYU and moved to the Albert Einstein College of Medicine and Montefiore Medical Center (collectively, "Montefiore"). JA721. Ostrer thereby extinguished any conceivable controversy that might have existed before.

Myriad and Montefiore have never communicated about the patents-in-suit; thus, Myriad never could have "chilled" any Montefiore scientist's testing. JA724-25. Ostrer's current claim to standing therefore reduces to a gripe that a licensing offer made to NYU in 1998 continues to "chill" his activities at an entirely different institution in 2013.

Ostrer has tried to avoid mootness by asserting that at Montefiore he retains the same readiness to perform genetic testing that he had while at NYU. JA722-23. But this makes the causal link to Myriad even more speculative than the hypothetical Myriad-NYU connection. Even if Ostrer was "once bitten" when he was at NYU, he is not entitled to claim that he is "twice shy" at Montefiore. *Already, LLC v. Nike, Inc.*, 133 S. Ct. 721, 730 (2013). Ostrer's assertion that Myriad's license offer to NYU somehow traveled with him to Montefiore because it was addressed to him individually (JA723) is incorrect. The letter was addressed to Ostrer solely as the NYU laboratory director, not in his personal capacity. JA94-95 (offering license to "NYU Medical Center"). The enclosure was a proposed license between Myriad and NYU, not with Ostrer personally. JA96, 98-99 (NYU is specified throughout; Ostrer, not once), 110 (signature blank for "NYU Medical Center," not Ostrer). Had NYU accepted the license offer, Ostrer could not have taken its rights with him when he left. Yet, by upholding Ostrer's standing, the Federal Circuit's ruling exposes patentees (and similar rights holders) to lawsuits by current or former employees of a license offeree, for the lifetime of the holder's right.

The Federal Circuit never addressed this, instead summarily denying Myriad's suggestion of mootness without any analysis. Pet. App. 25a n.6. The § 101 claim pressed by Ostrer assuredly holds some abstract, academic interest. But a court without jurisdiction must "put aside the natural urge to proceed directly to the merits." *Raines v. Byrd*, 521 U.S. 811, 819-20 (1997); *Already*, 133 S. Ct. at 726 ("courts have 'no business' deciding legal disputes or expounding on law in the absence of" a case or controversy).

The proper scope of § 101 as applied to isolated molecules should be addressed in a concrete controversy, not in an abstract policy vehicle of public-interest law firms. The vitality of companies and industries that this Court's judgment could affect should not depend on such a one-sided dispute. Accordingly, even were this Court to find that Ostrer presented a "real and immediate" controversy in 2009, such a controversy no longer exists, and this action should be dismissed as moot.[5]

II. THE COURT OF APPEALS CORRECTLY DETERMINED THAT MYRIAD'S CLAIMS ARE PATENT-ELIGIBLE

Applying the proper legal framework, as reflected in the USPTO's longstanding practice and even longer-standing case law, the Federal Circuit correctly determined that Myriad's claims are drawn to patent-eligible compositions of matter.

A. The Challenged Claims Are Chemical "Compositions Of Matter" Squarely Within § 101

Section 101 of the Patent Act, enacted in 1952, is a "threshold" provision, setting forth categories of patent-eligible subject matter. *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010). Section 101 has a broad scope, covering "anything under the sun that is made by man." *Chakrabarty*, 447 U.S. at 309. The statute provides in full:

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[5] If the Court vacates any prior decisions, it should include the district court's decision, because mootness resulted from the unilateral actions of Ostrer, who prevailed at the district court. *See U.S. Bancorp Mortgage Co. v. Bonner Mall P'ship*, 513 U.S. 18, 23 (1994).

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

35 U.S.C. § 101.

Myriad's claims are statutorily patent-eligible. Each claim is, on its face, to a chemical "composition of matter," or a "new and useful improvement thereof." Petitioners have never disputed this. C.A. App. 6911. Each claim recites "isolated DNA"—a physical, chemical compound (an acid) made up of nucleotides connected by a phosphodiester backbone. Pet. App. 14a. The molecules thus fall within the literal language of the statute.

B. The "Implicit Exception" To § 101 Excludes Only Things That Lack Human Invention

This Court has ruled that § 101 contains an "implicit exception[:] '[L]aws of nature, natural phenomena, and abstract ideas' are not patentable." *Mayo*, 132 S. Ct. at 1293. The touchstone of this implicit exception is the absence of human "invention."

This principle explains *Chakrabarty*, *Funk Brothers*, and *Mayo*. In *Chakrabarty*, the Court upheld the patent-eligibility of bacteria whose starting materials were in nature. The Court explained that the "relevant distinction" is whether the claims are directed to "human-made inventions."

447 U.S. at 313. Accordingly, *Chakrabarty* framed the § 101 question as whether the claimed composition is "a product of human ingenuity 'having a distinctive name, character and use'" from naturally-occurring starting materials. *Id.* at 309-10.

Chakrabarty distinguished the claims before it from those at issue in *Funk Brothers*, but it is clear that both cases turned on the presence (in *Chakrabarty*) or absence (in *Funk Brothers*) of human invention. As the Court of Appeals held (Pet. App. 49a-50a), *Funk Brothers*—which was decided when there was a single statutory provision governing both patent-eligibility and patentability (R.S. § 4886, codified at 35 U.S.C. § 31)—was a case involving the then-implicit requirement of "invention."[6] *Funk Bros.*, 333 U.S. at 131-32 ("a product must be more than new and useful to be patented; it must also satisfy the requirements of invention or discovery" (citing *Cuno Eng'g Corp. v. Automatic Devices Corp.*, 314 U.S. 84, 90, 91 (1941))). That requirement is now codified in § 103, with Congress "emphasiz[ing] 'nonobviousness' as the operative test of the section, rather than the less definite 'invention' language of *Hotchkiss [v.*

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[6] Whereas former R.S. § 4886 combined them, the 1952 Patent Act divided into separate statutory sections the requirements for patent-eligibility (§ 101) and patentability (§ 102 for novelty, § 103 for nonobviousness, § 112 for disclosure, etc.). Ostrer is thus wrong to describe *Funk Brothers* as a case involving "Section 101" (Pet. Br. 28), for § 101 did not exist in 1948. The United States makes the same error. U.S. Br. 14-15.

Greenwood, 52 U.S. (11 How.) 248 (1851)] that Congress thought had led to 'a large variety' of expressions in decisions and writings," including *Cuno's* "controversial phrase 'flash of creative genius.'" *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 15 (1966).

Applying the then-implicit invention principle, *Funk Brothers* pronounced that the claimed combination of bacteria, which maintained the same attributes as the preexisting bacteria in their uncombined form (the claim required the cultures to be "*unaffected by each other* in respect to their ability to fix nitrogen"), "d[id] not disclose an invention or discovery." 333 U.S. at 128 n.1, 132 (emphasis added). Instead, by attempting to claim only the combination of the natural properties of the bacteria, without "improv[ing] in any way their natural functioning" or enlarging "the range of their utility," *id.* at 131, the patentee in *Funk Brothers* "had discovered 'only some of the handiwork of nature,'" *Chakrabarty*, 447 U.S. at 310 (quoting *Funk Bros.*, 333 U.S. at 131). Dr. Chakrabarty's claim, by contrast, was "not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter" with "significant utility"—his "discovery [wa]s not nature's handiwork, but his own." *Id.* at 309-10. That constituted an invention under § 101.[7] *Id.* at 310.

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[7] *Chakrabarty's* discussion of the 1930 Plant Patent Act illuminates the meaning of invention under § 101. Prior to 1930, it was "belie[ved] that plants, even those artificially bred, were

Mayo similarly focused on invention. The Court concluded that patent claims covering methods of determining the proper dose of thiopurine drugs did not involve any human invention because "the claims inform a relevant audience about certain laws of nature," and further supplied only "well-understood, routine, conventional activity already engaged in by the scientific community . . . add[ing] nothing significant beyond the sum of their parts taken separately." 132 S. Ct. at 1298. Thus, there was no "invention." Indeed, the Court distinguished *Diamond v. Diehr*, 450 U.S. 175 (1980), by noting no evidence there that the method steps, "or at least the combination of those steps, were in context *obvious*, already in use, or purely conventional." 132 S. Ct. at 1299 (emphasis added).

In short, what § 101 requires, beyond the statutorily enumerated categories of eligible subject matter, is a modicum of "invention"—the "human ingenuity" referred to in *Chakrabarty* and the

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(continued...)

products of nature for purposes of the patent law." 447 U.S. at 311. By enacting the PPA, Congress "explained at length its belief that the work of the plant breeder 'in aid of nature' was [a] patentable invention." *Id.* at 312. The PPA's congressional reports stated that "a plant discovery resulting from cultivation is unique, isolated, and is not repeated by nature, nor can it be reproduced by nature unaided by man." *Id.* at 313. So, too, with the Myriad inventions—they are the work of the inventors in addition to nature, and their inventive compositions cannot be reproduced in nature unaided by man.

"inventive concept" in *Mayo.* Even then, the requirement must not be applied too rigorously, lest it swallow entirely the requirements of § 103 or run afoul of Congress's intent to bring more certainty to the longstanding but "less definite" "invention" requirement by codifying it as "nonobviousness." *Graham*, 383 U.S. at 14-15 (in § 103, Congress intended to abolish the "large variety of ways" courts had used to assess "invention"). The § 103 inquiry is more nuanced; it requires that "invention" be measured against prior art defined by § 102, looking to the level of skill in the art at the time of the claimed invention, the differences between the claimed invention and the prior art, and an important set of "secondary considerations" or "subtests of nonobviousness," to determine the nonobviousness *vel non* of a claimed invention. *Id.* at 17-18. Under § 103, the challenged molecules unquestionably represent a patentable invention in view of the differences between the newly created molecules and native DNA, the level of skill and knowledge in genetics in 1994, and the secondary considerations such as commercial success, upsetting the conventional wisdom, long-felt need, failure by others, and tribute from competitors. *See* pp. 2-10, *supra.*

The "invention" analysis of § 101, by contrast, parallels the eligibility threshold of copyright law, which requires authorial "originality"—defined as a "minimal level of creativity." *Feist Pub., Inc. v. Rural Tel. Serv. Co.*, 499 U.S. 340, 358-59 (1991) (calling this requirement "not particularly stringent"). Copyright, of course, shares an "historic kinship" and constitutional roots with patent law. *Sony Corp. of*

Am. v. Universal City Studios, Inc., 464 U.S. 417, 439 (1984). In copyright as with patent law, "facts and ideas" generally belong to the public, while original expressions "that display the stamp of the author's originality," like inventions demonstrating human ingenuity, are protectable. *See Harper & Row, Pub., Inc. v. Nation Enters.*, 471 U.S. 539, 547 (1985). Unlike copyright, however, patent law contains numerous other hurdles that an invention must surmount before a patent will issue.

C. The Identification, Definition, And Isolation Of A Particular Molecule With A Substantial Real-World Utility Is An "Invention" Under § 101

For over 30 years, the USPTO has applied § 101 and this Court's precedent to conclude that claims to isolated DNA molecules are "inventive" and therefore patent-eligible. This is an independent reason to uphold the patent-eligibility of Myriad's claims.

In 1982, less than two years after *Chakrabarty*, the USPTO granted the first human DNA-related patents. The issuance of these patents reflected an application of *Chakrabarty*, and a continuation of the more than 100-year-old practice of issuing patents on isolated forms of natural products. *See* pp. 2-5, *supra*. Patenting of DNA-related inventions has continued ever since, with the USPTO granting over 40,000 patents drawn to genetic material, almost 3,000 of which are directed to particular isolated DNA molecules. *See* Rogers, *supra*, at 19, 40; Pet. App. 61a-62a, 87a-88a, JA527-28.

One such patent was directed to "purified and isolated" forms of DNA encoding human erythropoietin ("EPO"), which are used to increase patients' red-blood-cell levels. Over 20 years ago, the Federal Circuit upheld the patent, distinguishing the claimed composition from what exists in nature: "It is important to recognize that neither Fritsch nor Lin invented EPO or the EPO gene. The subject matter of claim 2 was the novel *purified and isolated* sequence which codes for EPO . . . ." *Amgen*, 927 F.2d at 1206 (emphasis in original); *see also Amgen, Inc. v. Chugai Pharm. Co.*, No. 87-2617-Y, 1989 U.S. Dist. LEXIS 16110, at *89 (D. Mass. Dec. 11, 1989). This decision followed longstanding precedent by the Federal Circuit, its predecessor court (the C.C.P.A.), and courts evaluating patents prior to its creation, which have held that compositions that are isolated or extracted from natural products are patent-eligible (and patentable). *See* pp. 4-5, *supra*.

For its part, the USPTO drew on its unique knowledge of and familiarity with each of the roads at the intersection of science, technology, and patent law to reinforce the existing rule. Indeed, at several junctures, culminating in its 2001 *Utility Guidelines*, the USPTO evaluated its practice in light of relevant precedents, but never determined that isolated DNA molecules should be ineligible for patenting. *See* 66 Fed. Reg. at 1092. And even before the 2001 *Guidelines*, the USPTO had long issued patents on isolated natural products. *See id.* at 1093 ("Patenting compositions or compounds isolated from nature follow well-established principles, and is not a new practice"); Pet. App. 87a (the 2001 *Guidelines* were "simply a continuation of a longstanding and consistent policy of allowing patents for isolated natural products"); pp. 2-4, *supra*.

This Court has emphasized that a consistent and longstanding USPTO practice is entitled to substantial weight in interpreting and applying § 101. In *J.E.M.*, the Court observed that the USPTO applies "specific expertise in issues of patent law." 534 U.S. at 145; *see also Microsoft Corp. v. i4i Ltd.*, 131 S. Ct. 2238, 2242 (2011); *Dickinson v. Zurko*, 527 U.S. 150, 160 (1999). And in *Mayo*, this Court emphasized that it should "hesitate before departing from established general legal rules," and allow Congress to "craf[t] more finely tailored rules when necessary." 132 S. Ct. at 1305.

Respecting that role, and reiterating that § 101 has "broad scope and applicability," the Court in *J.E.M.* refused to deny patent protection to sexually reproduced plants where the USPTO had issued "some 1,800 utility patents" for approximately 16 years, with no "indication from either Congress or agencies with expertise that such coverage is inconsistent with [the governing statutes]." 534 U.S. at 144-45.

The case for continuing the established practice is even more compelling here than in *J.E.M.* The USPTO has issued almost *3,000* patents on isolated DNA molecules over the last *30* years, and, more broadly, over 40,000 DNA-related patents. Throughout, Congress has not altered the landscape or given any indication that the USPTO's practice should change. Rather, despite repeated attempts to change that longstanding practice, and fully aware of the debate being initiated by petitioners, their counsel, and others, Congress has declined to intervene. *See* Pet. App. 61a-62a, 92a-93a.[8]

Indeed, Congress has modified the Patent Act since the 2001 *Utility Guidelines*, including the recent America Invents Act, hailed as "the most significant reform of the Patent Act since 1952." Press Release, White House, President Obama Signs America Invents Act, Overhauling the Patent System to Stimulate Economic Growth, and Announces New Steps to Help Entrepreneurs Create Jobs (Sept. 16, 2011), www.whitehouse.gov/the-press-office/2011/09 /16/president-obama-signs-america-invents-act-overhauling-patent-system-stim (last visited Mar. 6,

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[8] "For example, Congress included, as part of the Patent Office's appropriations, language affirming the Patent Office's interpretation of § 101 to prohibit patents on human organisms. Consolidated Appropriations Act, 2004, Pub. L. No. 108-199, § 634, 118 Stat. 3, 101. Although Congress was aware 'that there are many institutions . . . that have extensive patents on human genes,' 149 Cong. Rec. H7248, H7274, it explicitly declined to implement legislation to 'affect any of those current existing patents.' 149 Cong. Rec. E2417-01. To the contrary, it made clear that the language related to 'human organisms' was not intended to change the Patent Office's policy with respect to claims to genes, stem cells, or other similar inventions. Far from oblivious to the patenting of genes, Congress introduced and declined to pass several bills which would put a moratorium on gene patents, authorize funding for the study of whether genes ought to be patentable, and exempt from patent infringement anyone who uses patented genes for non-commercial research purposes or medical practitioners who use genetic diagnostic tests." Pet. App. 92a-93a (Moore, J., concurring-in-part).

2013). Yet Congress made no modifications to § 101 that would affect the established legal rule, or the USPTO's conforming practice with respect to isolated DNA molecules.

In this way, this case presents the mirror image of *Mayo*. There, under the "established general legal rules," natural laws coupled with insignificant steps were not patent-eligible method claims. *Mayo*, 132 S. Ct. at 1305. Here, however, the established rule for over 100 years has been that isolates or extracts from natural materials that reflect human invention *are* eligible for patents, and the USPTO and courts have concluded for over 30 years that particular claimed isolated DNA molecules reflect patent-eligible human ingenuity. That, plus the interests in reliance and certainty engendered by the established rule, confirm that the Court should not disturb longstanding practice. *See J.E.M.*, 534 U.S. at 144-45.

Additionally, this established rule harmonizes with that of every other industrialized nation. Europe and Japan, for example, have officially pronounced their adherence to this rule. *See* EU Directive 98/44/EC, Art. 5(2), *available at* http://eur-lex.europa.eu/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=en&numdoc=31998L0044&model=guichett; Japanese Patent Office Examination Guidelines for Inventions in Specific Fields, Ch. 2, § 2.2.1(1), *available at* http://www.jpo.go.jp/tetuzuki_e/t_tokkyo_e/Guidelines/7_2.pdf; *see also* WTO Agreement on Trade-related Aspects of Intellectual Property Rights, Art. 27(1), *available at* http://www.wto.org/english/docs_e/legal_e/27-trips.pdf; JA567-68; Brief of *Amicus Curiae* The Institute of Professional Representatives before the European Patent Office (EPI) in Support of Neither Party (endorsing declaration at JA565-70).

The Federal Court of Australia, too, has endorsed this rule in rejecting an identical attack on Myriad's Australian patents. *See Cancer Voices Australia v. Myriad Genetics Inc.*, [2013] FCA 65 ¶ 108 (Austl.), *appeal docketed*, No. NSD35912013 (F.C.R. Mar. 4, 2013) ("[I]n the absence of *human intervention*, naturally occurring nucleic acid does not exist outside the cell, and 'isolated' nucleic acid does not exist inside the cell." (emphasis added)). Reversing the rule exemplified in the USPTO's *Guidelines* would set back the United States in an industry born and raised here, and often funded by the United States government. JA451-52.

Also, the longstanding rule reflected in the *Guidelines* makes sense. "[A]ll inventions at some level embody, use, reflect, rest upon or apply laws of nature, natural phenomena, or abstract ideas"; "too broad an interpretation of th[e] exclusionary principle could eviscerate patent law." *Mayo*, 132 S. Ct. at 1293. It is more judicious to determine patent-eligibility based on the presence of human ingenuity, rather than focus myopically on whether a natũral law or product was somewhere involved. "'While a scientific truth . . . is not a patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be.'" *Id.* at 1294 (quoting *Mackay*, 306 U.S. at 94).

As Judge Lourie explained, although isolated DNA molecules "are prepared from products of nature, so is every other composition of matter." Pet. App. 44a; Gunnar Samuelson & Lars Bohlin, DRUGS OF NATURAL ORIGIN: A TEXTBOOK OF PHARMACOGNOSY 19

(6th ed. 2009) ("[A]mong the modern drugs in use today about 40% are of natural origin," including "[a]pproximately 60% of anticancer remedies and 75% of drugs for infectious diseases"; "[m]any of the natural compounds are isolated from the producing organisms."). These products "are different from natural materials, even if they are ultimately derived from them." Pet. App. 45a. So, too, isolated DNA molecules differ from native DNA based on the contributions of human inventors.

D. Myriad's Claims Are Patent-Eligible

Adhering to the "established general legal rule," the Federal Circuit correctly concluded that Myriad's claims are patent-eligible.

1. Myriad's claimed molecules are human-made.

Myriad's claims are drawn to man-made compositions of matter (or at least man-made improvements thereof). Only by human intervention have the claimed molecules come about. For over a dozen years, Myriad's scientists and researchers engaged in intense effort, marked by novel scientific method and inquiry, to identify and define what came to be known as the BRCA1 and BRCA2 genes. Where others failed, Myriad identified the BRCA genes, and then, using information it had collected and discerned from studying the genes, characterized, defined, and isolated these particular molecules. The creation of new molecules never before available to the public is invention.

2. *Myriad made new molecules with great and valuable utility.*

These new molecules have "significant utility" not present in native DNA, but conferred precisely because of the Myriad inventors' ingenuity. *See Chakrabarty*, 447 U.S. at 310. Although the molecules were derived from natural materials, those materials in a state of nature provided none of the benefits of the claimed molecules. Only the isolated molecules can be used as, *e.g.*, probes and primers, allowing physicians and molecular biologists to determine a patient's predisposition to breast and ovarian cancers. These new attributes are the result of human ingenuity—the quintessential mark of patent-eligible subject matter. *See id.*; *see also* Dan L. Burk, *Anticipating Patentable Subject Matter*, 65 STAN. L. REV. ONLINE 109, 114 (2013) ("we want to reward inventors who provide access to molecules that were previously giving us no benefit"); Dan L. Burk & Mark A. Lemley, *Inherency*, 47 WM. & MARY L. REV. 371, 407 (2005) (similar). Without Myriad's work, there is no indication whether these particular molecules, and the valuable uses to which they have been put, would ever have come about.

E. The United States' Position Does Not Respect The Established Legal Rule Or Longstanding USPTO Practice

In its brief, the United States asserts that the eligibility line should be drawn between cDNA (eligible) and other isolated DNA molecules (not). *See* U.S. Br. 9. Over 30 years of precedent and practice have already drawn the line elsewhere—where human ingenuity causes a newly created, newly available composition to be isolated from natural, genomic material. This "established general legal rule"—not to mention the enormous reliance interests and property rights arising from that practice—is far more worthy of respect than the arbitrary line now being offered as a mere litigating position by the United States. *Cf. Bowen v. Georgetown Univ. Hosp.*, 488 U.S. 204, 212 (1988). The Federal Circuit unanimously upheld the patent-eligibility of cDNA claims, and the United States and other *amici* concur—but there is no defensible line to exclude other isolated DNA claims, for both came about through human intervention.

The United States is correct to conclude that claims drawn to cDNA molecules are patent-eligible. cDNA is a wholly synthetic molecule with a sequence nowhere found in native DNA. U.S. Br. 6, 18-19; Pet. App. 113a-14a; JA430-31. Indeed, the '282 patent specification makes clear that Myriad created SEQ ID NO:1 (*e.g.*, the isolated molecules of claim 2) as an artificial composite of fragmentary sequences isolated from various patient samples; it did not originate in a single human sample. JA772 (53:4-7 (describing "construction of a composite")). Fragments of this artificial composite (*e.g.*, the isolated molecules of claim 6) were then created and used by the Myriad inventors in further studies. JA772 (53:23-26); *see also* Pet. App. 81a-85a. Thus, because SEQ ID NO:1 in the '282 patent recites a particular man-made cDNA sequence, its claims 2, 6, and 7 are clearly patent-eligible. Likewise, because SEQ ID NO:1 in the '492 patent recites a particular cDNA sequence, its claim 7 is clearly patent-eligible. JA974-85, 1028.

There is, however, no basis for the United States' appellate lawyers to substitute their judgment for that of the USPTO, the agency with relevant expertise, in excluding other isolated DNA molecules from patent-eligibility. Even though the United States acknowledges that this Court's decision "will significantly affect the work of the [USPTO]," the agency "responsible for issuing patents" (U.S. Br. 1), the USPTO has not signed the brief (it did not sign the United States' briefs filed in the Federal Circuit, either). This is unprecedented in patent cases before this Court.[9] And the USPTO has not deviated from the *Utility Guidelines* in response to this litigating position. *See* Peter Loftus, *US Patent Office Keeps Status Quo Amid Gene-Patent Fight*, DOW JONES NEWS SERVICE, Nov. 2, 2010.

The Court should prefer the *Guidelines'* longstanding eligibility rule under which the isolation of a molecule with new utility represents sufficient human intervention to constitute patent-eligible subject matter.

First, isolated DNA molecules—including cDNA molecules—are "compositions of matter" within the language of the statute. *See* 66 Fed. Reg. at 1094 ("A purified DNA *molecule* isolated from its natural environment . . . is a chemical compound" (emphasis in original)).

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[9] At least since the Federal Circuit's 1982 creation, the USPTO has always joined the United States' brief in a patent case reviewed by this Court. *See, e.g.*, the United States' briefs in *Bowman v. Monsanto*, No. 11-796; *Mayo v. Prometheus*, No. 10-1150; and *J.E.M. Ag Supply v. Pioneer Hi-Bred International*, No. 99-1996.

Second, the USPTO's approach—but not the United States'—adheres to this Court's decisions, particularly *Chakrabarty*, and the legislative history indicating that "anything under the sun that is made by man" is eligible for a patent. In its *Guidelines*, the USPTO explains that, whether as "an excised gene" or "synthetic DNA preparations," isolated DNA molecules are patent-eligible because they "d[o] not occur in that isolated form in nature" and are "different from the naturally occurring compound." 66 Fed. Reg. at 1093. By their identification, definition, and excision, or by their synthetic preparation, the claimed compositions are man-made and inventive. The analysis that compels the patent-eligibility of cDNA compels the same conclusion as to other isolated DNA molecules.

Third, the USPTO's approach is consistent with longstanding interpretations of § 101. *See J.E.M.*, 534 U.S. at 145; *see also, e.g.*, *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993) (considering patentability of DNA-related claims and preemption concerns under § 112); *Amgen*, 927 F.2d at 1206. For more than 30 years, parties have relied on the USPTO's practice as reflected in the *Guidelines*. It is remarkable that no court, other than the district court here, has ruled a claimed composition patent-ineligible since § 101's 1952 enactment. Meanwhile, the USPTO's longstanding practice has seen no contrary action or indication by Congress.

Fourth, continuing to follow the established legal rule, set out in the USPTO's *Guidelines*, would avoid the *post hoc* scuttling of thousands of patents, and the property rights and reliance interests of inventors, investors, and industry that have allowed the United

States' biotechnology sector to grow and flourish. The stability and certainty of these interests has contributed to the public good in numerous ways—it has made new, life-saving products and environmental and consumer advancements available to the public; it has yielded a robust industry that contributes greatly to the national economy; and it has created countless jobs.

F. Ostrer's Approach Is Misguided

Although Ostrer gives a nod to whether a composition has an inventive concept (Pet. Br. 35-39; *Mayo*, 132 S. Ct. at 1294), he also proposes two other "ways" of determining patent-eligibility that misread the statute and this Court's precedent, ignore the USPTO's longstanding judgment, and diminish the clarity of the § 101 threshold. *E.g.*, Pet. Br. 23-24 (applying "inventive concept," "markedly different," and "preemption" tests). And in applying his cumbersome three-part test, he ignores and misrepresents the claim language and the science.

1. Ostrer misreads Chakrabarty and elides the differences that human ingenuity has imparted to isolated DNA molecules.

Ostrer makes much of the phrase "markedly different" from *Chakrabarty*. He catalogs certain similarities between the Myriad inventions and the native genetic starting materials, concluding that these similarities demonstrate that the isolated molecules are not "markedly different" from their starting materials. Pet. Br. 28-35; *accord* Brief for

Amicus Curiae Eric S. Lander in Support of Neither Party at 10-12 ("Lander Br.").[10] As an initial matter, the legal rule announced in *Chakrabarty* asks whether a claimed composition is "a product of human ingenuity 'having a distinctive name, character and use'" from a natural product. 447 U.S. at 309-10 (drawing from precedent). *Chakrabarty's* use of "markedly different characteristics" reflected not the legal rule, but the Court's factual description of *how different* Chakrabarty's bacterium was from bacteria in the wild.

Regardless, the proper inquiry focuses on the differences, not similarities. Because every patent-eligible composition of matter has its origins in nature, there will always be similarities to a natural substance. A patent-eligible baseball bat, though shaped and formed by human hands, will share the characteristics of the wood embedded in the tree from which the bat was formed. But the fact that the bat shares the properties of natural wood does not make the resulting, human-made product ineligible for patenting.

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[10] A word about Ostrer's terminology. When Ostrer speaks of a "product of nature," he includes within its scope products, like isolated molecules and cDNA molecules, whose starting materials originated in nature but have been manipulated into existence by humans. As Justice Frankfurter presciently observed, however, "[i]t only confuses" matters "to introduce such terms as 'the work of nature' and the 'laws of nature,'" because these are "vague and malleable terms infected with too much ambiguity and equivocation." *Funk Bros.*, 333 U.S. at 134-35 (Frankfurter, J., concurring). Ostrer's fluid use of the term "product of nature" to include such human-created compositions of matter seeks to capitalize on this ambiguity. *See id.* ("Arguments drawn from such terms for ascertaining patentability could fairly be employed to challenge almost every patent.").

Yet Ostrer utilizes the vagaries of his proposed tests by making essentially the same argument about isolated DNA molecules. Instead of acknowledging the differences—including the different utilities—that human inventors brought to the patented molecules, he improperly focuses on similarities between native DNA and isolated BRCA DNA molecules. But it is the differences that make a difference.

For instance, Ostrer repeatedly emphasizes that the "information content" of isolated DNA remains the same as native DNA, because "the gene sequence, the information it includes, and the laws it embodies are the same whether in or out of the body." Pet. Br. 9; *see also id.* at 30, 33, 35 (applying his fluid "markedly different" test). But nowhere does Ostrer acknowledge the differences that human intervention worked upon that molecule. A baseball bat can be used to hit a baseball because of the combination of the inherent qualities of the natural wood and the shape and size imparted to the bat by the inventor. Similarly, an isolated DNA molecule can be used as a cancer-mutation-detecting probe or primer because of natural qualities (their ordering of nucleotides, which in some cases other than cDNA molecules follows the ordering of native nucleotides) *in combination with* the inventors' scientific work and ingenuity in characterizing and defining the molecule's starting and end points, the severing of covalent bonds, and the removal of the specific defined molecule from other materials in its native environment to create new functionality as a probe or primer. Only because of the addition of human invention do these molecules exist to help patients chart their own course of medical treatments.[11] Even accepting the United States' argument that a patent should not be granted for discovering "useful properties of something that already exists in nature" (U.S. Br. 16-17), the useful properties of Myriad's isolated DNA molecules (as in *Chakrabarty*, but unlike in *Funk Brothers*) were not pre-existing. They exist only because of their characterization and isolation by human inventors.[12]

Ostrer thus mischaracterizes the Federal Circuit's opinion as "privileging the breaking of covalent bonds over all else." Pet. Br. 33. Not so. The court acknowledged that the claimed molecules exist in a "distinctive" form "from DNAs in the human body." Pet. App. 51a. As it explained, isolated DNA "consist[s] of just a fraction of a naturally occurring

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[11] Ostrer contends that isolated DNA nearing a gene's full length is not useful as a primer. Pet. Br. 34. This is irrelevant. Long strands of isolated DNA molecules are useful as probes and PCR templates. *See* pp. 7-8, *supra*.

[12] Ostrer further argues that isolated DNA "reinserted into the cell . functions as it did previously." Pet. Br. 9. This is both inaccurate and irrelevant. The likelihood of a reinserted DNA molecule landing in exactly the right spot and necessarily functioning exactly as it did in its native environment is minuscule and hypothetical. Regardless, a reinserted DNA molecule cannot diagnose cancer risk—the principal utility of the claimed isolated molecules.

DNA molecule," and the definition, isolation, and utility of the particular claimed molecule "results from human intervention." Pet. App. 51a-52a. Just as *Chakrabarty's* "markedly different" observation was a factual conclusion rather than a pronouncement of the § 101 legal inquiry, Judge Lourie's discussion of covalent bonds merely reflects the importance in his overall analysis of those structural differences between native and isolated DNA molecules. While he spoke forcefully in chemical terms, he understood the human manipulation required to create the claimed molecules. And Judge Moore's concurring opinion complemented Judge Lourie's by centering its attention on the different *utilities* imparted by such human invention. Pet. App. 80a-86a.

Under Ostrer's myopic focus on similarities to the exclusion of differences, *Chakrabarty* would have come out the opposite way. The bacterium in *Chakrabarty* was identical to the native one, P. aeruginosa, in innumerable ways. P. aeruginosa has one of the largest bacterial genomes of those sequenced to date. U.S. Patent No. 4,259,444; C.K. Stover et al., *Complete Genome Sequence of Pseudomonas Aeruginosa PA01, An Opportunistic Pathogen*, 406 NATURE 959 (2000). The size and complexity of P. aeruginosa's genome underlies its ability to thrive in a multitude of environments and its resistance to many drugs. Stover, *supra*, at 959. Chakrabarty's inventive act did not alter any of the preexisting 6.3 million base pairs of DNA in P. aeruginosa, or any of the bacterium's inherent capabilities.

Instead, by adding only two plasmids to P. aeruginosa's already-massive genetic content, Chakrabarty created a new bacterium. *Chakrabarty*, 447 U.S. at 310. That was so despite the fact that the two added plasmids contributed only a tiny fraction of the overall genetic content and capabilities of the modified bacterium. Thus, this Court's conclusion that the new bacterium had "markedly different characteristics" could not have been based solely on tallying the number of similar physical characteristics. The similarities *vastly* outnumbered the differences. The modified bacterium retained all of its original functions and properties and simply aggregated naturally-existing functionalities from other organisms. *See id.* But this Court correctly affirmed that even modest changes introduced by man may confer "significant" utilities that make a composition patent-eligible.

The claimed compositions here go even further beyond nature than Chakrabarty's invention did, by not just aggregating naturally-existing properties from several bacteria into one, but instead creating new utilities *where none existed before.* If the modest structural changes in Chakrabarty's bacterium so altered its utility as to give it a "distinctive name, character and use" and make the resulting product patent-eligible, 447 U.S. at 309-10, then surely Myriad's inventors' transformation of undifferentiated genomic material into DNA molecules that exist outside of the body with a different structure, and having additional, significant new utilities, is patent-eligible. And while extraction of random DNA may have been "well-understood, routine, conventional activity" in 1994, that is *not* what Myriad did or claimed. Instead, Myriad identified, characterized, and isolated *specific* molecular structures, never before known, used, or available.

When Ostrer does consider the differences, he concedes that isolated DNA has significant utilities that native DNA does not. Pet. Br. 2 (asserting that "it is not possible to study or use the genes unless they are isolated"); *id.* at 9, 41 (similar). Even though Ostrer is wrong to contend that one cannot study or look at genes without isolation (whole-genome sequencing does not involve isolation), he appropriately (if inadvertently) acknowledges that the different, human-imparted characteristics of isolated DNA molecules make them extremely useful in ways that genes in the body cannot possibly be.

Accordingly, Ostrer cannot analogize this case to *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1 (1931), which involved not the "implicit exception" to § 101, but the statutory definition of "manufacture" (not relevant here). There, the small amount of borax added to the rind of a fresh orange did not constitute a "manufacture" because it did not change "the name, appearance, or general character of the fruit." *Id.* at 12. It "remain[ed] a fresh orange fit only for the same beneficial uses as theretofore." *Id.* Here, by contrast, new structures and new "beneficial uses" arose from the addition of human ingenuity.

2. Ostrer's reliance on "preemption" is factually and legally unsound.

Ostrer's proposed test also relies on "preemption," but he uses that concept in such a heavy-handed way that it would destroy wide swaths of valid patents drawn to all kinds of inventions. Pet. Br. 40-48.

First, "preemption" is not a test for patent-eligibility. If it were, no patent could exist, for all patents are by their nature preemptive—they give their owners the right to exclude others. 35 U.S.C. § 154(a)(1). At most, preemption is an after-the-fact confirmation that a claimed invention is not patent-eligible because it would preempt use of noninventive ideas, laws, or phenomena. In *Mayo*, the Court's concern with preemption reflected the patent-ineligibility conclusion it had already drawn for a claim that added only well-understood, routine, conventional steps that doctors were already engaged in—a conclusion that does not apply here, where BRCA molecules had never before been known, used, or available. *See* 132 S. Ct. at 1301. Too much emphasis on preemption as even an alternative test could too broadly interpret the exclusionary principle, in violation of congressional intent to accord § 101 substantial scope. *Id.* at 1293.

Second, while Ostrer makes provocative assertions about the preemptive scope of Myriad's patent claims (*e.g.*, gene therapy, DNA-based computers), he has not based these assertions on fact. Any intelligent application of Ostrer's preemption test would require rigorous claim construction and a detailed infringement analysis comparing the claims to a specific device or activity, neither of which has occurred here. Because of the abstract, hypothetical nature of this lawyer-engineered "test case," there are no infringement claims or counterclaims to evaluate. Thus, Ostrer, unlike a party having real and immediate plans to engage in infringing activity (who would have an interest in construing the claims narrowly lest they cover that activity), freely urges that Myriad's claims are broad, expansive, and would cover every kind of genetic research. This goes beyond any reasonable reading of the patents. *See* pp. 50-55, *infra*.

Third, it is clear that the claims—properly understood—do not preempt ineligible subject-matter or other, competitive technologies. One example of something Ostrer contends is preempted (Pet. Br. 14-15, 31, 44), but which is clearly not, is whole-genome sequencing. In 2001, seven years after Myriad's inventions, the human genome project used random sequencing—without "isolation" of particular DNA molecules—to determine and publish the entire human genome sequence. In 2007, the entire genetic makeup of Dr. James Watson, an *amicus* supporting Ostrer, was characterized using whole-genome sequencing without isolation; Watson himself was found to harbor a BRCA mutation. *See* BIO-IT WORLD, *Project Jim: Watson's Personal Genome Goes Public*, www.bio-itworld.com/newsitems/2007/may/05-31-07-watson-genome (last visited Mar. 6, 2013). A host of other technologies—gene expression profiles, untargeted single-molecule sequencing, and protein-truncation testing—sequence DNA or detect genetic mutations without isolation.[13] Ostrer's contrary assertion (Pet. Br. 9) cites only the district court's observations, which were unsupported by any evidence. *See, e.g.*, Pet. App. 342a (incorrectly positing that "a time may come when the use of DNA for molecular and diagnostic purposes may not require" isolation; as demonstrated, that time has long since come).

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[13] *See, e.g.*, http://www.nanoporetech.com/technology/analytes-and-applications-dna-rna-proteins/dna-sequencing-applications; http://www.nanoporetech.com/technology/analytes-and-applications-dna-rna-proteins/dna-an-introduction-to-nanopore-sequencing; http://pacificbiosciences.com; http://www.ncbi.nlm.nih.gov/pubmed/10425032; http://www.ncbi.nlm.nih.gov/pubmed/19668243 (all last visited Mar. 5, 2013);

Nor have Myriad's patents inhibited research, denied patients access to their genetic material or information, engaged in monopolistic pricing, prevented other laboratories from providing second opinions or conducting BRCA clinical tests, created a faulty test, or caused any of the other "chilling effects" Ostrer alleges. Pet. Br. 2-3, 7-9, 43-48. The claims do not preempt, preclude, or prohibit others from researching BRCA genes or creating and offering new and improved tests, and Myriad's extensive patient services and "gold standard" BRAC*Analysis*® have significantly furthered, not limited, patient care. *See* pp. 8-10, *supra*.

(continued...)

Christopher M. Holman, *Will Gene Patents Derail the Next Generation of Genetic Technologies?: A Reassessment of the Evidence Suggests Not*, 80 UMKC L. REV. 563, 579 (2012); Int'l Patent Application No. PCT/US2008/080358, Publication No. WO/2009/052417 (published Apr. 23, 2009) (Wendy S. Rubinstein, applicant).

3. *Ostrer ignores J.E.M. and the Utility Guidelines.*

Understandably, Ostrer prefers ambiguous tests like "product of nature," "markedly different," and "preemption" over the clear rule reflected in the *Utility Guidelines.* Indeed, he does not acknowledge the USPTO's longstanding practice as reflected in the *Guidelines* until the very end of his brief. And even there, he accuses the USPTO's exhaustive, expert, consistent, and coherent understanding of the law of being "remarkably free of any analysis." Pet. Br. 54. The *Guidelines* on their face belie this accusation—they address, in detail, the reasons for the USPTO's conclusions that particular isolated DNA molecules satisfy § 101, buttressed by legal citations and references to the Office's longstanding practice, dating back over 100 years. The Court should by now be familiar with Ostrer's counsel's pattern of directing rash (and unsupported) insults towards the USPTO and the work of its public servants.[14]

The USPTO's "specific expertise in issues of patent law," *J.E.M.*, 534 U.S. at 145, and its consistent and longstanding practice of issuing patents to particular isolated DNA molecules, should lead this Court to respect the *Guidelines* as a proper application of § 101 and this Court's decisions, most notably *Chakrabarty*. Ostrer's blithe attempt to sweep away the *Guidelines* by contending that they are "not binding on this Court" (Pet. Br. 54) is unresponsive. The *Guidelines*' force does not depend on their "binding" nature, but upon the USPTO's expertise in this area, *J.E.M.*, 534 U.S. at 145, and the fact that this "highly visible decision has led to the issuance of [thousands of] utility patents for [isolated DNA molecules]. Moreover, the PTO, which administers § 101 . . . recognizes and regularly issues utility patents for [isolated DNA molecules]." *Id.*

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[14] Ostrer's counsel is fond of such rhetoric, calling patents today "nothing more than some overly worked patent examiner's decision to allow claims requested by an applicant," Br. of Public Patent Foundation as *Amicus Curiae* in Support of Petitioner at 2, *FTC v. Actavis, Inc.*, No. 12-416 (U.S. Jan. 29, 2013), and accusing the USPTO "of being a rubber stamp" and granting patents for financial, rather than legal, reasons, Br. of Public Patent Foundation as *Amicus Curiae* in Support of Petitioner at 6, *Already*, 133 S. Ct. 721 (No. 11-982).

There is more. In this case—as in *J.E.M.*—"Congress has not only failed to pass legislation indicating that it disagrees with the PTO's interpretation of § 101; it has even recognized the availability of utility patents" upon genetic material. *Id.* Judge Moore's opinion canvassed this Congressional recognition and approval. *See* p.31 n.8, *supra*. Lacking any "indication from either Congress or agencies with expertise that such coverage is inconsistent with [§ 101]," *J.E.M.*, 534 U.S. at 144-45, this Court should uphold the line drawn by the USPTO's *Guidelines* as a proper interpretation and application of the statute.

4. *Ostrer relies on claim constructions never sought or made in the lower courts, and otherwise does violence to the claim language.*

Ostrer's arguments rely, in substantial part, on efforts to have this Court ignore claim terms or construe claim language for the first time. These arguments are not fairly included within the question presented, and they seek to do considerable violence to the claim language.

"Isolated." Ostrer calls this important term "clever draftsmanship" that has duped the USPTO. Pet. Br. 27; *accord id.* at 2; U.S. Br. 20 (addressing the claims "[a]bsent the 'isolated' limitation"). The most glaring example of his effort to ignore this claim term appears in his framing of the question presented—whether "human genes" can be patented. Pet. Br. 11. But, by their express terms, the claims cover "isolated" DNA molecules, not "human genes." *See also* 66 Fed. Reg. at 1093 ("A patent on a gene covers the isolated and purified gene but does not cover the gene as it occurs in nature"; "[p]atents do not confer ownership of genes.").

By avoiding the claim term "isolated," Ostrer fails to engage each claim "as a whole." *Diehr*, 450 U.S. at 192. More significantly, by minimizing this claim term as though it does not appear in the claims, Ostrer seeks to eliminate the very aspect of the claims that confirms the application of "human ingenuity," and that imparts the differences between the claimed isolated molecules and the naturally-existing, genomic DNA that is bound up in the body.

For instance, Ostrer and his *amici* contend that there are fragments of genetic material in the body with broken bonds that are "identical to the fragments created by Myriad when it isolates the gene." Pet. Br. 11; *see also id.* at 9-10, 32 (contending that "the gene separated from the chromatin can be found in the body" and that "gene fragments exist in the body," including in maternal plasma); Lander Br.

12-18 (similar). But fetal DNA floating within a mother's blood, or DNA floating within a person's own blood, is not "isolated" within any conceivable interpretation of the claims, because it remains in its natural environment. It has not been removed or "separated from other cellular components which naturally accompany" it, as the claims require. JA755 (19:8-19). Nor is there any record support that these fragments in the body have the same sequences specified in Myriad's claims.

Likewise, Ostrer contends that the claimed cDNA molecules of claim 2 of the '282 patent are patent-ineligible because they exist in the body as "pseudogenes." Pet. Br. 51. But such pseudogenes have significant structural differences from the molecules of claim 2 and are not "isolated," and thus do not make available to the public the diagnostic benefits of the claimed cDNA molecules.

"DNA." Ostrer also tries to expand the claims beyond the scope of § 101 by broadening the meaning of "DNA." According to Ostrer, "DNA" as used in the claims "is defined broadly," and thus the claims "are not limited to any particular molecular structure" and thus include all variations and mutations of the sequences recited in the claims. Pet. Br. 6, 13-14, 30-31; *accord, e.g.*, *Amicus Curiae* Brief for Academics in Law, Medicine, Health Policy and Clinical Genetics in Support of Neither Party at 33.

Ostrer never made this claim-construction argument before, so it is not properly before this Court. In any event, since there is no explicit definition of "DNA" in the patents, the term is properly defined by its plain and ordinary meaning to one of ordinary skill in the art: as the macromolecule deoxyribonucleic acid. *See* JA755 (19:1-11); Pet. App. 308a. More importantly, the claims do not use "DNA" in a vacuum, but instead modify that word with additional terms that make absolutely clear how specific and focused these claims are—"isolated" molecules having the particular "SEQ IDs" that are claimed.

Ostrer's references to other defined terms in the specifications (terms not used in the claims),[15] and to passages in the specifications that generally describe the invention (*e.g.*, JA748, 755 (6:26-28, 19:51-53, 53-57)), cannot be imported into the claims. It is the claims that measure the metes and bounds of the inventors' invention and the patent grant. *See* 35 U.S.C. § 112; *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 29 (1997). Again seeking to shift the ground upon which this case has been litigated, Ostrer asserts a too-broad, never-before-argued claim interpretation.

"Coding for." Ostrer also contends that, by reciting DNA "coding for" the specific strings of A, T, C, and G nucleotides in the SEQ ID set forth in a claim, the claims cover mere genetic information—any person's genetic information with that sequence or as represented in a printout of a patient's DNA sequence. Pet. Br. 34-35. This does further violence to the claim language. The claims are not directed to

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[15] *E.g.*, "BRCA1 Locus" and other similar terms (JA755 (19:35-40, 20:34-35)); "substantial homology" (JA757 (24:62-63)); and "fragment," "portion," and "segment" (JA755, 758 (19:1-5, 20:63-65, 25:33-35)).

functions, information, or printouts. They claim precisely defined molecules—compositions of matter—having a specific, non-naturally-occurring structure.[16] Here, again, the *Utility Guidelines* answer Ostrer's charge: "Patents do not confer ownership of . . . genetic information, or sequences"; "descriptive sequence information alone is not patentable subject matter." 66 Fed. Reg. at 1093; *see also Cancer Voices Australia*, [2013] FCA 65 ¶ 109.

Use. Ostrer has never disputed that the claims have substantial utility unavailable before the invention. He nonetheless seeks to make something of the fact that the claims "are not limited to any particular use." Pet. Br. 17; *accord id.* 34 & n.9. There is a serious question whether the claims would cover the activities cited by Ostrer, and, in the important case of whole-genome sequencing, it is clear they would not. But that is irrelevant. A patent need only describe a single utility to support § 101's utility requirement. *See In re Ziegler*, 992 F.2d 1197, 1200 (Fed. Cir. 1993). Moreover, by statute, *see* 35 U.S.C. § 112(a) (formerly ¶ 1), an invention's use must be disclosed in the specification, not in the claims themselves. *See id.* A patentee is not required to specify an invention's use within the claim.[17]

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[16] The "coding for" limitation reflects structural, not functional, attributes. *See In re Deuel*, 51 F.3d 1552, 1555, 1557-58 (Fed. Cir. 1995) (claims reciting an isolated DNA sequence "encoding" a particular sequence claimed "new chemical entities in structural terms"). Similarly, the SEQ IDs represent the composition claimed. *See* 37 C.F.R. §§ 1.821-1.825; MPEP § 2420 *et seq.*

5. *Ostrer relies on distortions of the record and "facts" that are not consistent with science.*

In numerous additional ways, Ostrer mischaracterizes and distorts the record and science, exacerbating his misunderstanding of the claims' patent-eligibility.

a. Ostrer makes various incorrect assertions about genes and native DNA and their supposed similarities to Myriad's molecules. He describes a gene as "a segment of chromosomal DNA," implying that native DNA is naturally broken up into discrete, individual genes, just like the claimed isolated compositions. Pet. Br. 4 & n.1. A gene, however, is a human-defined region(s) of a chromosome—not a single, self-contained "segment" ready for picking. JA228-29, 378, 418-19 468; *see also* p. 7, *supra*.

b. Ostrer's and his *amici*'s analogies to gold, kidneys, or leaves removed from their "natural environment" are factually inapt. Pet. Br. 34; U.S.

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[17] Ostrer also asserts that claim 2 of the '282 patent is "useless to Myriad" without covering any mutations or variations of that sequence. Pet. Br. 14-15. That is incorrect. Claim 2 is a "consensus sequence," synthetically created by Myriad after studying a large number of individuals to identify a sequence that ordinarily does not have mutations. *See* JA771-74. Thus, when the coding regions of an individual's DNA differ from the consensus sequence of claim 2, a predisposition to cancer is likely—making the claim a very valuable contribution.

Br. 22. After removal, the gold remains gold, the kidney remains a kidney, and the leaf remains a leaf. As the Court of Appeals explained, "[a] kidney is an organ, not a well defined composition of matter or an article of manufacture specified by § 101." Pet. App. 60a. Here, by contrast, the DNA is not merely removed from the body but is "isolated"—*i.e.*, human manipulation created specific chemical compositions that differ structurally from what exists in nature, providing the molecules with new properties that permit them to operate differently than their starting materials. While the United States minimizes this transformation as "snipped" ends having "no functional consequences" (U.S. Br. 22), such dismissive rhetoric severely understates the inventive activity. The isolated DNA molecules are designed by humans to "zero-in" on the BRCA DNA in the patient sample, so that their "snipped" reactive ends direct the amplification of the target DNA. This was the product of creative, human ingenuity.

c. Ostrer greatly distorts the factual record of Myriad's inventions, giving only lip service to "Myriad's work." Pet. Br. 41 n.10. Contrary to that characterization, Myriad's inventions were universally hailed. The European Patent Office called Myriad's inventions "a major breakthrough which was not obvious to the skilled person." Board of Appeal of the European Patent Office, No. T 1213/05 at 69-70 (2007), *available at* www.epo.org/law-practice/case-law-appeals/pdf/ t051213eu1.pdf; *see also* JA490 (Myriad's invention was "a scientific accomplishment that required many inventive steps, not the least of which was to contradict the scientific dogma of the time"); *accord*

JA478-90, 746-47, 851-52, 945-46. Even Myriad's competitors acknowledged its breakthrough. JA485, 501-02.

6. Ostrer conflates patentability with patent-eligibility.

This case is solely about patent-eligibility under § 101 (Pet. 19, JA54 (disclaiming reliance on any provision of the Patent Act other than § 101)), yet Ostrer repeatedly challenges the claims' "patentability"—the province of other sections of the Act. Pet. Br. i, 2, 20-21, 23, 25-29, 32, 34, 48, 51, 53-55. He even recasts his legal theory as broadly embracing whether "human genes" are "patentable." Pet. Br. i. Since the complaint was limited to § 101, the record is necessarily incomplete on any other issues. The Court should not mistake the many patentability arguments that appear in Ostrer's brief (and the faulty factual assertions presented in support) as relevant to eligibility.

For instance, Ostrer asserts that Myriad's claims have "extraordinary breadth" and "reac[h] a huge number of compositions." Pet. Br. 15, 31; *accord id.* at 14-15, 15-16, 37, 41. Claim breadth and clarity are patentability considerations evaluated under § 112, which demands that a claimed invention be "fully and particularly described" and "distinctly claimed." *Bilski*, 130 S. Ct. at 3225; *see also Festo Corp. v. Shoketsu Kinzoku Kagyo Kabushki Co.*, 535 U.S. 722, 736 (2002). Section 112 adequately protects against indefinite patents. *See, e.g.*, *Fiers*, 984 F.2d at 1171

("Claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement"). This is no concern of the § 101 threshold.[18]

Likewise, despite acknowledging that "cDNA is generally made in the laboratory," Pet. Br. 51, Ostrer insists that cDNA is not "patentable" because "cDNA is identical to DNA except the non-coding regions have been removed," *id.* at 49. This relates to the novelty requirement of § 102, not patent-eligibility under § 101's invention principle. *See Diehr*, 450 U.S. at 190 (novelty "is wholly apart from whether the invention falls into a category of statutory subject matter").

Similarly, whether the differences between man-made isolated DNA molecules (including cDNA molecules "made in the laboratory") and native DNA render the former ultimately patentable is most appropriately assessed under § 103's nonobviousness requirement. That inquiry requires a sensitive, fact-dependent analysis, *see* p. 27, *supra*, but plaintiffs developed none of those facts in the district court. The undisputed facts available to the Court all point in favor of nonobviousness, *id.*, particularly in light of the fact that plaintiffs would have borne the burden of proof by clear-and-convincing evidence. 35 U.S.C. § 282; *i4i*, 131 S. Ct. at 2242; *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 417 (2007).[19]

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[18] Ostrer also suggests that the claims are ineligible because they cover an entire class of mutations without a corresponding disclosure. Pet. Br. 14-15, 31, 37. That argument is irrelevant to § 101. Moreover, the rule under § 112 is that "disclosure of a species may be sufficient written description support" for a claim to a genus. *Bilstad v. Wakalopulos*, 386 F.3d 1116, 1124 (Fed. Cir. 2004).

Myriad is prepared to defend against any patentability challenges on an adequately-developed record. This case does not afford that opportunity. *See Diehr*, 450 U.S. at 191 (limiting inquiry where case presented "only the question of whether respondents' claims fall within the § 101 categories of possibly patentable subject matter").

* * * *

Patentability challenges, under §§ 102, 103, and 112, typically present legal issues based on an extensive evaluation of underlying facts. *See i4i*, 131 U.S. at 2253 (Breyer, J., oncurring). It is easy to see how a § 101 determination could depend on resolving factual disputes, just as the similar question of "nonobviousness" presents underlying factual questions under § 103. (Certainly, the number of misstated facts relied upon by Ostrer suggests that factual questions could overwhelm a § 101 inquiry.) Accordingly, the Court should view § 101 challenges as ones where the challenger bears the burden of proof, and must establish any underlying facts by clear and convincing evidence. That is unnecessary here, however. The undisputed material facts established on the summary-judgment record demonstrate that Myriad's patent claims to isolated DNA molecules are human-made compositions—the product of an "inventive concept," *see Mayo*, 132 S. Ct. at 1294.

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[19] Judge Bryson, dissenting as to the non-cDNA claims, cited to research by one of Myriad's principal competitors for BRCA1, who was "the first to map a BRCA gene to its chromosomal location [17p21]." Pet. App. 99a. This might be relevant to novelty and prior invention under § 102, and nonobviousness under § 103, but not eligibility under § 101.

G. The Court Should Not Undo The "Established General Legal Rule"

Given long-established practice and precedent, this Court's guidance in *Mayo* applies with full force: Courts should not "depar[t] from established general legal rules lest a new protective rule that seems to suit the needs of one field produce unforeseen results in another." 132 S. Ct. at 1304-05. Yet Ostrer and his *amici*, many of whom have an interest in competing with Myriad by using Myriad's own inventions, ask the Court to unravel over 30 years of reliance—in the form of investment and advance across multiple industries benefiting millions of patients and consumers, as the purpose of the Patent Act contemplates. The Act accomplished that here, incentivizing and protecting Myriad's inventions, and with Myriad using its inventions to develop life-saving tests to the benefit of the public.

Perhaps sensing the extent of the damage their theories would impose, Ostrer and others suggest that the Court could cabin the outcome to only isolated *human* DNA molecules. Pet. Br. i; *e.g.*, Lander Br. 5. There is no principled way to distinguish between isolated "human" DNA molecules and isolated plant and animal DNA molecules, which are themselves used for untold agricultural, livestock, consumer, and biofuel products. For *all* of these industries, "the legitimate expectations of inventors in their property," and the consequent benefits to the public, would be destroyed if the established legal rule were changed. *Festo*, 535 U.S. at 739; *Warner-Jenkinson*, 520 U.S. at 32 n.6 (changing "the rules of the game now could very well subvert the various balances the PTO sought to strike when issuing the numerous patents which have not yet expired and which would be affected by [the Court's] decision").

In short, "[a]ny recalibration" of the longstanding rule should "remai[n] in [Congress's] hands." *i4i*, 131 S. Ct. at 2252; *see also Chakrabarty*, 447 U.S. at 317 (policy matters are "for resolution within the legislative process after the kind of investigation, examination, and study that legislative bodies can provide and courts cannot").

III. THE CLAIMS CONFORM WITH THE FIRST AMENDMENT

In barely two pages, Ostrer seeks to reinstate his First Amendment challenge. Pet. Br. 55-58. That argument is waived. Though plaintiffs' complaint included a First Amendment claim, their challenge to the composition claims here was limited to patent-eligibility. Pet. i. Even the body of their petition included only one paragraph and one general citation regarding the First Amendment (Pet. 30-31), and their reply in support of certiorari nowhere mentioned the First Amendment. That claim is not "fairly included" within the question presented—*see* this Court's Rule 14.

Besides, the claims do not violate the First Amendment for the same reason that Ostrer's § 101 challenge is incorrect. *See* pp. 39-60, *supra*. The claims are to physical compositions, not abstract thoughts or information; thus the claims cannot "restrict access to information" or speech. Pet. Br. 56.

CONCLUSION

This case should be dismissed for lack of jurisdiction. If the Court were to reach the merits, the judgment of the Court of Appeals should be affirmed.

Respectfully submitted,

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March 7, 2013

REPLY
BRIEF

RECORD AND BRIEFS

FOR ARGUMENT

No. 12-398

Supreme Court, U.S.
FILED
APR 2 - 2013
OFFICE OF THE CLERK

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,
Petitioners,

—v.—

MYRIAD GENETICS, INC., ET AL.,
Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES
COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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INTRODUCTION

Myriad identified two genes that exist in every person. It did not create, invent, or design the genes by "isolating" them. Its patents claim products and laws of nature and thus are invalid under Section 101.

Myriad does not dispute that BRCA gene fragments appear in the body, with covalent bonds broken and separated from material such as chromatin with which they are normally associated. Resp'ts Br. 51-52. It has thus essentially abandoned any defense of the insignificant structural differences asserted by the Federal Circuit majority. In addition, although Myriad emphasizes the use of genes as probes and primers, it concedes that the claims are not limited to probes or primers. *Id.* at 8, 42. What remain are Myriad's arguments that it extracted the genes from the body and added to the storehouse of knowledge. The first would not distinguish patenting a gene from patenting a kidney. The second is precisely rejected by the law or product of nature doctrine.

Myriad dismisses this Court's product and law of nature doctrine. It expands the Section 101 inquiry by repeatedly asserting that the difficulty of the task and the value of the result are relevant considerations. It contracts the inquiry by asserting that factors considered by this Court, such as whether what is patented has markedly different characteristics or preempts use of laws and products of nature, are irrelevant. Myriad also improperly places heavy reliance on the PTO's practice of granting gene patents. None of Myriad's arguments comports with this Court's precedents.

The assertions of Myriad's *amici* largely rest on the fear that a ruling in Petitioners' favor might prevent useful patents on tests, drugs, other DNA-related compositions such as recombinant DNA, or patents limited to particular uses. *See, e.g.*, Br. for Amici Curiae Genentech, Inc. et al. in Support of Resp'ts, Mar. 14, 2013 ("Genentech Br."). This case does not challenge the patent-eligibility of recombinant DNA (DNA that results from choosing fragments from genes or chromosomes that do not appear together in nature and stitching them together), recombinant therapeutic proteins, or genetically engineered antibodies. These patents are on naturally-occurring genes.

Finally, Myriad argues again that the case should be dismissed based on standing. That effort should be rejected.

ARGUMENT

I. ISOLATED DNA IS A PRODUCT AND LAW OF NATURE, NOT AN INVENTION.

A. DNA

Myriad has used four different arguments to explain why it believes "isolated" DNA is not a product or law of nature but instead its invention: isolated DNA has a different structure than DNA in the body, isolated DNA has a new function, isolated DNA is the result of extraction, and patents on isolated DNA add to scientific knowledge. None is persuasive; none establishes that Myriad designed, created, or invented the DNA.

Different Structure From DNA Found In Nature. Myriad argues that "isolated" DNA has a different structure from DNA in the body. Resp'ts Br. 44. Myriad concedes that isolated DNA has the same nucleotides in the same order as genomic DNA and that isolated DNA conveys the same information and represents the same laws of nature as genomic DNA. *Id.* at 41. Myriad offers no specific structural alteration other than to refer to the structural differences identified by the Federal Circuit; *i.e.*, that in separating a gene from its chromosome, a covalent bond is broken. *Id.* at 42. Petitioners and *amici* have established that fragments of the BRCA genes with covalent bonds broken do exist in nature. Pet'rs Br. 10-11; Br. for Amicus Curiae Eric S. Lander in Support of Neither Party 12-18, Jan. 31, 2013 ("Lander Br."). Myriad does not dispute that. Resp'ts Br. 51-52. Because Myriad offers no other structural distinctions between "isolated" DNA and DNA, it has effectively conceded that none exists.

New Function. Myriad argues that "isolated" DNA can perform functions that DNA cannot perform.[1] Myriad is in effect arguing that it may obtain a patent on a product or law of nature itself if it finds a new use for it. Under this theory, Section 101 would not prohibit someone from obtaining a patent on gold if she found a new use for gold. As a matter of law, that argument is incorrect. *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289, 1293 (2012).

If one finds a new use for a product of nature, one may seek a method patent on that new use. Myriad, in fact, has claims to DNA for particular uses. *E.g.*, 2J.A. 823 (claim 16 of patent '282 on use of DNA as primer). Petitioners have not challenged those claims and the validity of such claims is not before the Court. The claims in this case are to the product of nature itself and not limited to any single use.

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[1] Resp'ts Br. 7, 8, 35, 41-44.

Myriad relies heavily on an argument that the patented genes acquire new functionality because they could potentially be used as probes or primers.[2] However, Myriad concedes that full-length genes, which are unquestionably included within its claims, cannot be used as primers. Resp'ts Br. 42. And Myriad concedes that none of the challenged claims is limited to the use of the DNA as a probe or primer, but instead reach any use. *Id.* at 8, 42. Thus, Myriad's alleged new functionalities do not justify the patent claim.[3]

Extraction.[4] Myriad argues that "isolated" DNA is different from DNA because it has been extracted from the body. Under this theory, Hans Dehmelt, who won the Nobel Prize for being the first to isolate a single electron from an atom, could have patented the electron itself. A kidney removed from the body (or gold extracted from a stream) would be patentable subject matter. Myriad's only response is to say that a kidney is an "organ" and DNA is not an "organ." Resp'ts Br. 56. But that distinction has no legal bearing. For the reasons stated more fully in Petitioners' opening brief, Pet'rs Br. 26-48, Myriad's patent claims to isolated DNA cover products and laws of nature and are therefore invalid.

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[2] The district court provided clear definitions of probes and primers. Pet. App. 264a-65a.

[3] Myriad only briefly alludes to its use of "isolated" DNA for purposes of diagnosis, perhaps because diagnosis is impossible if the isolated DNA is not identical to the DNA in the body. Moreover, "isolated DNA," standing alone, cannot diagnose cancer risk, Resp'ts Br. 42, n.12 – many more steps must be taken.

[4] Like the district court, petitioners use the term "extraction" rather than the term "isolation." Pet. App. 263a. Myriad has often used the term "isolation" to include both separation of the gene from the chromosome and also removal from the body. As noted above, Myriad did not refute that separation of the gene from the chromosome and other material such as chromatin does not distinguish "isolated" DNA from DNA. Accordingly, the only portion of the term "isolation" that is left is extraction from the body.

Myriad's argument also fails to acknowledge that scientists have been extracting genes, including BRCA1 and BRCA2, from the body and other matter since at least the 1970's. Lander Br. 8 n.4 (explaining how fragments of the entire genome were extracted and collected).

Adding to the Storehouse of Knowledge. The only remaining argument that could support Myriad's patents is that Myriad added valuable information to the storehouse of knowledge. The cornerstone of the Section 101 doctrine, however, is that adding to the storehouse of knowledge is an insufficient basis for receiving a patent. *Funk Bros. Seed Co. v. Kalo Inoculant Co.,* 333 U.S. 127, 130 (1948); *Bilski v. Kappos,* 130 S. Ct. 3218, 3225 (2010); *Mayo,* 132 S. Ct. at 1301-02. Thus, the fact that Myriad scientifically annotated the genome by locating the particular nucleotides that form the BRCA genes does not satisfy Section 101.

Although Myriad claims an invention, the words it uses to most commonly describe its accomplishment are not about invention. The verbs

Myriad uses to describe its work are "identify," [5] "define,"[6] "locate,"[7] or "characterize."[8] Einstein "identified," "defined," and "characterized" the relationship between matter and energy, but his discovery was not patentable. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980). An astronomer who "identifies" or "locates" a new object in space and then "defines" or "characterizes" it as a comet has not turned that comet into her invention. The first scientists to isolate lithium from its naturally-occurring metallic form were not entitled to a patent on an element of the periodic table. Pet. App. 104a-05a.

B. The Expansiveness of Myriad's Claims Is Evidence of Their Ineligibility Under Section 101.

Myriad argues that a patent claim's scope is only relevant to the written description requirement of Section 112. But claim scope is directly relevant to many of the requirements of the Patent Act, including Sections 101, 102, and 103.

Myriad's claims reach the genes of every woman, man, and child in America. The moment any person's BRCA gene is removed, Myriad has exclusive rights to it even if Myriad never previously isolated DNA having that sequence and did not and could not know its sequence. The claims are expansive precisely because their bounds are defined by nature. The common link among the hundreds of millions of different compositions that are claimed is that they occur in nature and serve the functions dictated by nature. Likewise, the claims to any DNA coding for the BRCA protein and over any mutation that causes cancer are defined by nature. These are not claims written to specify particular DNA or cDNA that is used as a primer or probe to target particular genetic mutations, or that has been changed to produce a therapeutic protein. They are claims to products and laws of nature.

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[5] Resp'ts Br. 2, 6, 34, 38, 45.

[6] *Id.* at 2, 6, 7, 34, 38, 41, 43.

[7] *Id.* at 6.

[8] *Id.* at 34, 41, 42, 45.

C. cDNA

1. *The patent-eligibility of cDNA is not at issue in this case.*

This case should be resolved without reaching the patent-eligibility of cDNA, because none of the claims is limited to only cDNA. For the first time, Myriad argues that some of its claims are so limited. Resp'ts Br. 11. This argument is inconsistent with the patents' language. The patents define DNA as used in the claims to include both DNA and cDNA. *See, e.g.*, Patent '282, 19:14-18, 19:51-53, 2J.A. 755.

Myriad argues that the compositions it now claims are limited to cDNA differ from genomic DNA because cDNA is "synthesized in laboratories and exclude certain regulatory and other non-protein-coding sequences (introns) found in native DNA and include only protein-coding DNA (exons)." Resp'ts Br. 12. Petitioners do not dispute that cDNA has these attributes; however, Myriad did not limit the cited claim (or any of the challenged claims here) to such attributes. In addition, the claims use the term "has" ("...wherein said DNA has the nucleotide sequence…"). That term has a specialized meaning in patent law, generally interpreted to mean "including but not limited to." U.S. Patent and Trademark Office, Manual of Patent Examining Procedure § 2111.03, at 2100-45 (8th ed. Rev. 9 2012) (citing *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1573 (Fed. Cir. 1997) (applying the expansive meaning of the term to cDNA)).

Myriad attempts, nonetheless, to limit claim 2 of the '282 patent, 2J.A. 822, to these attributes by citing the "wherein" clause which references the sequence. Resp'ts. Br. 12. The "wherein" clause, however, does not reference any descriptive text adjoining the sequence. Thus, the only proper construction of claim 2 is that it covers "isolated DNA [with] the nucleotide sequence set forth." This language does not limit the claim to cDNA and covers any DNA that has the sequence given. To analogize, assume the patent claim at issue was to "an automobile of the color in figure X," which depicts a truck with red paint. Myriad would argue that the claim is limited to trucks with red paint, but the claim references only the color set forth in figure X, not the automobile type. If Myriad wanted to claim *cDNA* with the sequence that is described, it could (and should) have claimed "the cDNA molecule with the sequence…"

Finally, Myriad argues that claim 6 of the '282 patent, 2J.A. 822, is limited to cDNA. Resp'ts Br. 12. But claim 6 covers any nucleotide sequence containing 15 or more nucleotides from SEQ. ID NO:1, and 15 nucleotide (and longer) sequences from SEQ. ID NO:1 are found throughout genomic DNA. 1J.A. 631-34, 662-72; Pet. App. 114a-16a. *See also*

Jeffrey Rosenfeld & Christopher E. Mason, *Pervasive Sequence Patents Cover the Entire Human Genome*, 5 Genome Med. 27 (2013) (showing that 15-nucleotide sequences of BRCA1 match at least 689 other genes, that all human genes contain at least one patented 15-nucleotide sequence, and that current gene patents cover at least 41% of all known genes). To argue that claim 6 is limited to cDNA is simply to ignore its plain language and the facts.

2. *If the Court concludes it must reach the issue of the patent-eligibility of cDNA, it should find cDNA unpatentable.*

Myriad argues that because cDNA is generally made in a laboratory, it is patent-eligible. Resp'ts Br. 6-7. Petitioners anticipated and responded to this flawed argument. Pet'rs Br. 51-52.

The DNA that Myriad asserts is cDNA contains the identical genetic sequence as the coding regions in the naturally-occurring DNA of every person. 2J.A.755. The key difference between genomic DNA and cDNA is that the latter is complementary to natural mRNA, wherein the body has removed the non-coding regions. That removal occurs in the body by natural processes. Myriad has nothing to do with it. Pet'rs Br. 49-50.

In the laboratory, Myriad takes naturally-occurring mRNA from the body and simply relies on the natural binding properties of nucleotides to assemble the DNA. *Id.* Imagine the mRNA as magnets positively charged by nature. All that humans do is to add magnets negatively charged by nature (ordinary nucleotides). The nucleotide's natural properties cause them to link and the result is called cDNA.[9]

cDNA is quite distinct from recombinant DNA, which is created when a geneticist selects cDNA or DNA fragments from different sources and intentionally stitches them together. Lander Br. 20. Any therapeutic application of cDNA requires further altering cDNA to create recombinant DNA. *Id.* But cDNA that simply mirrors naturally-occurring mRNA is a product of nature and a basic scientific tool; preempting its use impedes innovation. *See Mayo*, 132 S. Ct. at 1293.

II. MYRIAD ATTEMPTS TO SALVAGE ITS CLAIMS BY DISTORTING THE LEGAL STANDARD APPLICABLE TO SECTION 101, IN VIOLATION OF THIS COURT'S PRECEDENTS.

Myriad offers its own more expansive legal standard for Section 101: whether the composition is a result of "human intervention," emphasizing the degree of effort involved and the value of the products and laws of nature uncovered. Myriad also seeks to minimize factors identified by this Court such as preemption. Finally, Myriad deems dispositive that the Patent Office has approved of the compositions at issue. Resp'ts Br. 34, 49-50. Each of these arguments ignores, and in some instances rejects, the principles laid out in the Court's most relevant cases. *See, e.g., Mayo*, 132 S. Ct. 1289;

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[9] The binding properties of nucleotides are not magnetic, but the qualities are analogous. It is thus inaccurate to say that Myriad "designed" or "created" either DNA or cDNA. Resp'ts Br. 6, 34.

Chakrabarty, 447 U.S. 303; *Funk Bros.*, 333 U.S. 127; *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1 (1931).

A. Invention Under Section 101 Cannot Be Reduced To Mere "Human Intervention."

In deciding whether a patent is valid under Section 101, the Court has not simply asked whether humans were involved in the purported invention, but instead examined the characteristics of what was patented and the extent to which the patent preempts use of a product or law of nature. *Mayo*, 132 S. Ct. at 1294; *Chakrabarty*, 447 U.S. at 308-10; *Funk Bros.*, 333 U.S. at 129-32; *American Fruit Growers*, 283 U.S. at 11-13. The Court has scrutinized whether the underlying product or law of nature has been transformed into something with a "distinctive name, character [and] use," and "markedly different characteristics from any found in nature." *Chakrabarty*, 447 U.S. at 309-10.

Myriad nonetheless argues that "markedly different characteristics from any found in nature" is not part of the legal analysis, Resp'ts Br. 40. *Compare with* Pet. App. 50a, 76a, 107a. Myriad further asserts that the Section 101 inquiry must focus on whether there are any differences between the patented composition and nature, no matter how overwhelming the similarities may be. Resp'ts Br. 40. As discussed in Section I, *supra*, the "differences" referred to by Myriad are unsupported by science or unspecified in the challenged patent claims. In any case, the Section 101 inquiry has never been limited in the manner Myriad now proposes. Under Myriad's view, the Court would have upheld the patents on the *American Fruit Growers* fruit and the *Funk Brothers* bacteria; both were in some small measure different from the fruit and bacteria strains as they existed prior to the patentee's activity, but both were deemed unpatentable subject matter.

Instead of applying the Court's precedents, Myriad attempts to reduce the analysis to mere human intervention or human ingenuity. Defying more than 150 years of case law, Myriad states: "It is more judicious to determine patent-eligibility based on the presence of human ingenuity, rather than focus myopically on whether a natural law or product was somewhere involved." Resp'ts Br. 33.[10] But Section 101, as enforced by this Court, requires more than human ingenuity or intervention to establish patent-eligibility.

The electron, gold, and lithium examples illustrate this point: patent-eligibility does not rest on the difficulty or cost of defining the composition or on its value. *See Parker v. Flook*, 437 US 584, 593 (1978) (Section 101 determination must precede novelty and utility inquiries). Myriad highlights the praise it received after sequencing BRCA1 and BRCA2. Resp'ts Br. 5-6, 56-57.[11] The discovery deserves praise, but patents are not granted based on recognition, costs, or hard work. Incorporating such considerations into Section 101 would eviscerate this Court's long-standing precedent. Many compositions resulting from serious investment, such as drugs and new genetic technologies, deserve patent protection, but that is because they represent true inventions and not because resources were poured into their development.

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[10] Myriad compounds its error by misconstruing *Chakrabarty*'s partial quotation of legislative history, Resp'ts Br. 16, without acknowledging that Congress clearly recognized the statutory limitations to patent-eligibility: "A person may have 'invented' a machine or a manufacture, which may include anything under the sun made by man, but it is not necessarily patentable under Section 101 unless the conditions of the title are fulfilled." H.R. Rep. No.1923, 82d Cong., 2d Sess., 6 (1952).

[11] Myriad fails to give due credit to the ground-breaking work of Dr. Mary-Claire King and her team, who identified the locus of the BRCA1 gene and similarly received wide acclaim. Kevin

B. Myriad's Patents Preempt Uses Of Laws And Products Of Nature.

The Court has made clear that patents cannot preempt all uses of any laws or products of nature or abstract ideas without running afoul of Section 101. *See Mayo,* 132 S. Ct. at 1293; *Bilski*, 130 S. Ct. at 3225; *Chakrabarty*, 447 U.S. at 313; *Funk Bros.,* 333 U.S. at 130-31; *O'Reilly v. Morse*, 56 U.S. 62, 113-18 (1853); Pet. Br. 40. The "preemption of nature" inquiry unearths the extent to which the patent interferes with using a law or product of nature. Myriad minimizes the relevance of preemption, even though "[t]he Court has repeatedly emphasized this last mentioned concern, a concern that patent law not inhibit further discovery by improperly tying up the future use of laws of nature." *Mayo*, 132 S. Ct. at 1301.

Davies & Michael White, *Breakthrough: The Race to Find the Breast Cancer Gene* 2-6 (1996). The gene "came to be known as the 'BRCA1 gene,'" Resp'ts Br. 6, because Dr. King named it so. Others made significant contributions as well. *See, e.g.*, Kenneth J. Abel et al., *A Radiation Hybrid Map of the BRCA1 Region of Chromosome 17q12-q21*, 17 Genomics 632 (1993).

All of the evidence presented in this case supports the conclusion that Myriad's patents preclude others' use of laws and products of nature. Because DNA must be isolated in order for clinicians and researchers to use the gene and the information it contains, the patents stop others from basic scientific activity. The patents are the reason why no other laboratory in the U.S. can conduct full sequencing of these genes, even using testing methods other than the one employed by Myriad. *E.g.*, Pet. App. 37a. The patents have been decried by famed geneticists like declarant John Sulston and *amici* James Watson and Eric Lander, all leaders of the Human Genome Project. *See* 1J.A. 129-40; Br. of James D. Watson Ph.D. as Amicus Curiae in Support of Neither Party 19, Jan. 31, 2013 ("Watson Br.") ("A human genome cluttered with no trespassing signs granted by the Patent Office inhibits scientific progress, particularly the development of useful tests and medicines in areas requiring multiple human genes"); Lander Br. 25 (these "claims erect an insurmountable barrier to studying these DNA sequences, with serious consequences for innovation in medicine"). They stand in the way of genetic testing companies like *amici* GeneDx and InVitae, which are among the many laboratories developing new technologies for sequencing human genes. *E.g.*, Br. of GeneDx and Law Professors as Amicus Curiae in Support of Pet'rs, Jan. 30, 2013; Br. of Amicus Curiae InVitae Corp. in Support of Pet'rs, Jan. 31, 2013. And they pose a serious barrier to developments in personalized medicine that could benefit us all. *E.g.*, Br. of Amici Curiae Am. Medical Ass'n et al. in Support of Pet'rs, Jan. 29, 2013 ("AMA Br."); Br. for Canavan Foundation et al. as Amici

Curiae in Support of Pet'rs, Jan. 31, 2013 ("Canavan Br."); Br. of AARP as Amicus Curiae in Support of Pet'rs, Jan. 31, 2013 ("AARP Br.").

Myriad attempts to refute this point by focusing on how it *chooses* to enforce its patents, not on the rights granted through the patents. Thus, it claims that because it has not enforced its patents against some scientists who engaged in research relating to the BRCA genes, there is no preemptive effect. Resp'ts Br. 48. Myriad may well decide not to sue certain researchers, particularly when their work may further knowledge about the genes and thus increase the value of Myriad's genetic testing services. But Myriad's argument ignores the authority it has and the documented chilling effect these patents have had as they influenced scientists' decisions about where to focus their work. 1J.A. 162-66, 219-24, 715-18; AARP Br. 3-6; Watson Br. 14, 16-22; Rosenfeld & Mason, *supra* at 5.

Myriad similarly asserts that whole genome sequencing or other sequencing methods would not violate its patents. That argument ignores the definition of "isolation" in its patents or as construed by the lower courts. Whole genome sequencing requires fragmenting DNA, including breaking its covalent bonds. Michael L. Metzker, *Sequencing Technologies – The Next Generation*, 11 Nature Reviews 31 (2010). The technician will inevitably "isolate" the BRCA1 and BRCA2 genes as she sequences the entire genome. Myriad cannot sidestep the fact that whole genome sequencing would violate its patents by claiming it would not enforce them against those testing methods (or not enforce it so long as the results are not shared with a patient, a condition it has placed on researchers, *e.g.*, 1J.A. 59, 164, 171, 173, 186-97). *Cf.* Robert L. Green et al., Am. Coll. Med. Genetics, *ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing* 13, 25 (2013) (recommending that laboratories disclose BRCA genetic information when obtained incidentally through genome sequencing). The forbearance Myriad has expressed in this litigation offers no protection to any laboratory that wants to provide BRCA results as a part of a whole genome clinical assay. Similarly, Myriad refers to other testing methods that do not sequence DNA at all, but instead measure other biological phenomena such as gene expression. Because they do not involve the natural phenomena at issue here – a patient's BRCA genetic sequence – their existence is irrelevant to whether the patents preempt laws and products of nature.

C. PTO Practice Does Not Provide The Legal Framework To Decide The Question Presented.

Myriad further departs from this Court's precedent by arguing that PTO practice should be "an independent reason" to uphold patents under Section 101. Resp'ts Br. 28. PTO practice, however, has never been a decisive factor in determining patent-eligibility. *See, e.g.*, *Mayo*, 132 S. Ct. at 1304-05 (disapproving patents granted by PTO); *Chakrabarty*, 447 U.S. at 306 (upholding patents rejected by PTO). Indeed, the PTO routinely granted patents similar to the ones this Court found invalid in *Mayo*. Following this Court's ruling, the PTO issued two guidance documents to its examiners to inform them how *Mayo* should change their patent-eligibility determinations. Andrew H. Hirshfeld, U.S. Patent & Trademark Office, *Preliminary Guidance to Patent Examining Corps on Supreme Court Decision in* Mayo Collaborative Services v. Prometheus Laboratories, Inc. (2012); Andrew H. Hirshfeld, U.S. Patent & Trademark Office, *Memo to Patent Examining Corps on 2012 Interim Procedure for Subject Matter Eligibility Analysis of Process Claims Involving Laws of Nature* (2012) ("Interim Procedure"). For example, the PTO noted that contrary to prior PTO practice, *Mayo* treated the correlation between metabolite levels, resulting from the administration of a drug, and drug efficacy as a law of nature. Interim Procedure at 7, n.5. The PTO further predicted that "[a]dditional guidance from the courts on how to identify laws of nature may be forthcoming in cases like *Myriad*." *Id.* Thus, the PTO, industry, and relevant stakeholders understand and expect that the courts have an important role in resolving Section 101 questions.

The legal framework for deciding patent eligibility is Section 101 and this Court's precedents. As the United States explains in its brief, the PTO's Utility Guidelines do not have the force of law. U.S. Br. 27-28. And contrary to Myriad's representations, Resp'ts Br. 29, the PTO has never taken a blanket position approving the patent-eligibility of isolated natural products. Indeed, the 1889 case of *Ex Parte Latimer* illustrates how the government recognized early on the dangers of allowing such patents. 1889 Dec. Comm'r Pat. 123 (1889). The Commissioner of Patents found that even though the fibers at issue were obtained by freeing them from the pine needle and removing extraneous matter, and thus made more useful for mankind, they were not patentable. To rule otherwise would mean that "patents might be obtained upon the trees of the forest and the plants of the earth, which of course would be unreasonable and impossible." *Id.* at 126.

The issue of isolated DNA's patent-eligibility was not presented before any court until this case. The lower court decisions cited by Myriad, Resp'ts Br. 4-5, did not involve Section 101 or dealt with *purified* (referring to concentrated) compositions that were transformed to serve new functions, such as triggering therapeutic response; the patents therefore did not preempt examining or measuring the product of nature itself. Likewise, the legislative history that Myriad and its *amici* point to does not support upholding these patents. Congressional inaction on isolated DNA cannot support an inference that Congress endorsed the PTO's practice of issuing these DNA patents. *Rapanos v. United States*, 547 U.S. 715, 750 (2006) (plurality opinion); *Solid Waste Agency v. U.S. Army Corps of Eng'rs*, 531 U.S. 159, 169-70 (2001). *Cf. J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 145 (2001) (referring to congressional enactment of legislation confirming that plants are patentable).[12]

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[12] Similarly, Myriad's references to international law are inapposite. The Agreement on Trade-Related Aspects of Intellectual Property ("TRIPS") allows governments to exclude patents on the grounds of public interest, the patent systems in other countries vary widely, and most allow for greater research than is permitted in the U.S.. TRIPS, art. 27; *Cancer Voices Australia v. Myriad Genetics Inc.* (2013) FCA 65 (Austl.) (court decision based on Australian patent law, which is "quite different" from American law); 1J.A. 699-702. Myriad does not have the same rights to BRCA in other countries. *See, e.g.*,

III. A RULING FOR PETITIONERS WILL HAVE POSITIVE RESULTS FOR INDUSTRY AND PATIENTS.

This Court has frequently said that patents on products or laws of nature can have severely negative effects on the advancement of science. *E.g.*, *Mayo*, 132 S. Ct. at 1293 ("monopolization of those tools through the grant of a patent might tend to impede innovation more than it would tend to promote it"). There is ample support in the record for that conclusion with regard to DNA. *See, e.g.*, 1J.A. 695-710; Pet'rs Br. 42-48. The claims also have had devastating effects on patients. Pet'rs Br. 7-9. *See, e.g.*, AMA Br. 6-13; Lander Br. 23-26; 29; Canavan Br. 10-16.

Myriad's *amici* do not seriously dispute these facts. Instead, they voice concern that a ruling for Petitioners might prevent patents on things other than "isolated DNA." For example, some fear that the Court's decision might reach patents on recombinant DNA. *See* Genentech Br. 4-5. Recombinant DNA is DNA in which the scientist has joined two or more DNA sequences that are not found together in nature in order to achieve certain effects. The recombinant DNA sequence and function are designed by the scientist, as opposed to the DNA in this case, where both the sequence and function are determined by nature. As many of the *amici* acknowledge,

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1J.A. 136-37, 213-14; Bryn Williams-Jones, *History of a Gene Patent: Tracing the Development and Application of Commercial BRCA Testing*, 10 Health L.J. 123, 143 (2002) (in Europe and Canada, Myriad was either unsuccessful in obtaining the broad rights granted in the U.S. or its patents were disregarded by the government).

recombinant DNA is the "invention" that enables the production of the novel proteins used to treat many diseases, and most economically valuable patents in the biotechnology industry are on recombinant DNA. *See id.* at 6-7; Lander Br. 20; Watson Br. 18, 21.

A ruling for Petitioners in this case would not preclude patenting of recombinant DNA. Petitioners' arguments pertain only to "isolated DNA," which is required to diagnose an individual's own genetic susceptibility to cancer and other conditions. Indeed, Myriad's BRCA1 and BRCA2 patents, particularly claims 5 and 6 of patent '282, 2J.A. 822, preclude all others from using BRCA1 or BRCA2 fragments to create recombinant DNA. Thus, a ruling for Petitioners would not jeopardize patents on recombinant DNA and would in fact facilitate that option.

Some of Myriad's *amici* express concern about the ruling's effects on the development of therapeutic drugs. First, it should be noted that this case does not challenge patents on drugs. Myriad did not develop a new drug and did not go through FDA trials or approval prior to offering testing. *See* Frederic M. Scherer, *The Economics of Human Gene Patents*, 77 Acad. Med. 1348, 1351-52 (2002) (biotechnology industry's profits and expenses relate to drug sales and FDA approvals, not genetic testing). Second, to the extent that *amici* argue that patenting isolated DNA was the first step toward their eventual development of drugs (and thus such patents must be upheld), the contention either seeks special treatment for biological products of nature, a proposition this Court recently rebuffed, or completely rejects the constitutional underpinnings of the product and law of nature doctrine. *Mayo*, 132 S. Ct. at 1305. Locking up a product of nature such as two human genes through patents might very well benefit the patentholder, but at the expense of forcing the public to rely on a single entity to fully investigate the wide range of scientific, medical, and commercial potential for those genes.

To the extent Myriad or its *amici* are arguing that the patents in this case were necessary to create an incentive to search for the BRCA1 and BRCA2 genes or to commercialize a test for the genes, the record is clear that they were not. 1J.A. 244-60. Other scientists, including those who did not want patent exclusivity, were looking equally vigorously for the genes, *id.* at 136-38, 248-50, and other laboratories had begun testing for mutations until Myriad forced them to stop. Pet. App. 21a-22a, 37a. Myriad's monopoly on the BRCA genes has allowed it to dictate the quality and provision of BRCA genetic testing and to control the scientific knowledge about the genes, thereby limiting medical practice, chilling research, and restricting access to information crucial to women's health.[13] Patent protection at the level of the gene (versus on actual tests, recombinant DNA, etc.) is simply unnecessary to spur innovation in diagnostics. Rep. of the Sec'y's Advisory Comm. on Genetics, Health, and Soc'y, *Gene Patents and Licensing Practices and their Impact on Patient Access to Genetic Tests* 31 (Apr. 2010). In other contexts, gene patents have *interfered* with the availability of testing. AMA Br. 10.

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[13] Myriad's *amici*'s arguments that the claims' harmful effects could be ameliorated are based on speculation, rather than the law, as evidenced by the enforcement of the BRCA patents. There is no compulsory licensing regime, and compulsory licenses have never been ordered following *eBay, Inc. v. MercExchange, L.L.C.*, 547 U.S. 388 (2006). Similarly, the government has never exercised march-in rights over patents in which it has an interest. And the "research exception" to patent infringement is extremely narrow. *Madey v. Duke Univ.*, 307 F.3d 1351 (Fed. Cir. 2002) (noting any activity in furtherance of "legitimate business," regardless of profit motive, falls outside the exception).

A ruling for Petitioners in this case would not preclude patenting of recombinant DNA, new drugs, or new methods of diagnosis and/or treatment. Instead, it would ensure that human genes – the blueprint for human biology – can be accessed by all scientists and medical professionals working in diagnostics, biotechnology, pharmaceuticals, and other fields.[14]

IV. PETITIONERS HAVE STANDING.

For the fifth time in this case, Myriad argues that Dr. Ostrer does not have standing. Resp'ts Br. 17-22. The Federal Circuit formally rejected the argument three times. Pet. App. 25a, n. 6, 32a, 40a-42a. In twice granting the Petition in this case, this Court at least implied that it found the argument unpersuasive. The Court should reject it.

The Federal Circuit specifically found that:

- Myriad threatened to sue Dr. Ostrer. *Id.* at 33a-34a.

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[14] As noted, Petitioners have not challenged claims limited to the use of DNA as a probe or primer. Section I, *supra*. Similarly, Petitioners have not challenged claims limited to diagnostic kits. *See, e.g.*, 2J.A. 823, cl. 18.

- Dr. Ostrer seeks to engage in infringing activities, *id.* at 32a-33a, and Dr. Ostrer "states unequivocally that he will immediately begin such testing . . ." *Id.* at 36a.
- Dr. Ostrer "has the resources and expertise to immediately undertake clinical BRCA testing. . ." *Id.* at 35a-36a.
- "Myriad's active enforcement of its patent rights forced Dr. Ostrer, as well as every other similarly situated researcher and institution to cease performing the challenged BRCA testing services . . ." *Id.* at 37a.
- "[T]he relevant circumstances surrounding Myriad's assertion of its patent rights have not changed despite the passage of time," *id.* at 36a, "Myriad and Ostrer have not altered their respective positions," *id.* at 37a, and "nothing in the record suggests that any researcher or institution has successfully attempted to compete with Myriad, or that Myriad has in any way changed its position with regard to its patent rights." *Id.* at 37a.

Given these facts, Dr. Ostrer clearly has standing. ***MedImmune, Inc.** v. **Genentech, Inc.***, 549 U.S. 118 (2007). Myriad's argument – that no one has standing unless Myriad has recently and personally threatened them with suit for infringement – is inconsistent with this Court's standing jurisprudence. *See* Cert. Pet. 32-35.[15]

CONCLUSION

For the foregoing reasons, the patent claims should be held invalid.

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Dated: April 2, 2013

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[15] The Federal Circuit did find that the other petitioners lacked standing, Pet. App. 41a, and this Court denied certiorari on that issue.

AMICUS
CURIAE
BRIEF

RECORD
AND
BRIEFS

Supreme Court, U.S.
FILED
JAN 31 2013
OFFICE OF THE CLERK

No. 12-398

In the Supreme Court of the United States

ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,
PETITIONERS

v.

MYRIAD GENETICS, INC., ET AL.

ON WRIT OF CERTIORARI
TO THE UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE IN SUPPORT OF NEITHER PARTY

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QUESTION PRESENTED

Whether human genes are patent-eligible subject matter under 35 U.S.C. 101.

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INTEREST OF THE UNITED STATES

This case presents the question whether certain human genetic materials are patent-eligible subject matter under 35 U.S.C. 101. The Court's resolution of that question will significantly affect the work of the United States Patent and Trademark Office (PTO), which is responsible for issuing patents. 35 U.S.C. 2(a)(1). The question presented is also of substantial importance to several other federal agencies, including the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention.

STATEMENT

1. Section 101 of the Patent Act of 1952, 35 U.S.C. 1 *et seq.*, provides that an inventor may obtain a patent on "any new and useful process, machine, manufacture, or

composition of matter, or any new and useful improvement thereof, * * * subject to the conditions and requirements of this title." 35 U.S.C. 101. The provision thus "defines the subject matter that may be patented." *Bilski* v. *Kappos*, 130 S. Ct. 3218, 3225 (2010). Congress cast the provision "in broad terms to fulfill the constitutional and statutory goal of promoting 'the Progress of Science and the useful Arts.'" *Diamond* v. *Chakrabarty*, 447 U.S. 303, 315 (1980); see *J.E.M. Ag Supply, Inc.* v. *Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 130-131 (2001).

Section 101 is subject, however, to an "important implicit exception": "[l]aws of nature, natural phenomena, and abstract ideas are not patentable." *Mayo Collaborative Servs.* v. *Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1293 (2012) (citation and internal quotation marks omitted) (*Mayo*). Such "manifestations of * * * nature" are "free to all men and reserved exclusively to none." *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948).

2. a. Deoxyribonucleic acid (DNA) is a molecule that encodes the instructions required by living cells to produce the proteins essential for their structure and function. Pet. App. 257a-260a. DNA directly or indirectly controls nearly every aspect of an organism's physiology. The basic structure of DNA comprises two strands of four different repeating chemical units—adenine (A), thymine (T), guanine (G), and cytosine (C)—known as "nucleotides" or "bases." *Id.* at 257a. These strands bind together and twist into a distinctive double helix. *Id.* at 258a. The four standard nucleotides are chemically paired such that cytosine always binds with guanine, and adenine with thymine. *Ibid.* Because of the predictable way in which nucleotides pair, it is possible to

infer from a nucleotide sequence on one strand of DNA the corresponding nucleotide sequence with which it may bind. *Ibid.* Likewise, it is possible to infer from the nucleotide sequence of a DNA molecule the structure of the corresponding protein that the DNA segment "encodes," *i.e.*, instructs the cell to build. *Ibid.*

An organism's complete set of DNA is its "genome." Pet. App. 259a n.6. With qualifications not relevant here, a "gene" is any section of DNA that, through its nucleotide sequence, governs the expression of a particular protein. *Id.* at 258a. Only certain portions of a gene's nucleotide sequence, known as "exons," code for the protein that the gene expresses. *Ibid.* The remaining portions of the gene include non-protein-coding regulatory regions governing the manner and timing of a cell's protein production, as well as non-coding intervening sequences known as "introns." *Ibid.*

b. Within a human body, DNA ("native DNA") is packaged into chromosomes and bound with chromosomal proteins. Pet. App. 262a. DNA can be extracted from its cellular environment through "any number of well-established laboratory techniques." *Id.* at 263a. A particular DNA segment of interest, such as a gene, can then be excised from the extracted material. The result of this laboratory process—a DNA molecule excised from the genome and separated from its cellular environment—is commonly termed "isolated DNA." See, *e.g.*, J.A. 755 (U.S. Patent No. 5,747,282, col. 19, lines 8-18 (filed May 5, 1998) ('282 patent)). Once a DNA segment has been isolated, it can be studied and exploited in a laboratory. For instance, isolated DNA can be used as diagnostic tools that target and bind to particular DNA segments—"probes"—and as aids in sequencing and reproducing DNA—"primers." See Pet. App. 264a-265a.

Scientists can also manufacture a variety of artificial DNA molecules that alter or recombine raw genetic materials in new and useful ways. For example, "complementary DNA" (cDNA) molecules are synthetic molecules built by scientists to include, in a single contiguous DNA segment, only the exons of a naturally occurring gene, without the introns and regulatory regions that are normally interspersed with exon sequences in genomic DNA. See Pet. App. 267a-269a. cDNA molecules are synthesized by taking advantage of the process by which DNA directs the creation of protein in a cell. During that process, the DNA double helix unzips, and a new molecule, ribonucleic acid (RNA), is formed by an enzyme that copies the now-single strand of DNA, matching the strand's nucleotides with complementary nucleotides. The introns are then spliced out of the RNA molecule, and the exons are joined in a contiguous strand, leaving a molecule known as "messenger RNA," or "mRNA." *Id.* at 266a. When this process occurs within a cell, the mRNA then provides instructions "for the assembly of a protein." *Id.* at 267a.

In order to create cDNA, scientists use mRNA for a different purpose: to generate a new DNA molecule that contains nucleotide sequences complementary to the mRNA's nucleotides. The resulting cDNA molecule includes the same exon sequences present in the original DNA strand but lacks the DNA's intron and regulatory sequences. Pet. App. 268a-269a. Because they contain protein-coding nucleotides in uninterrupted form, cDNAs have a variety of uses. For instance, they can be inserted into a cell in order to cause it to express a protein of interest. *Id.* at 269a.

3. Since the early 1980s, the PTO has issued patents on a wide range of engineered DNA molecules and useful genetic methods. In 1982, the PTO began to issue patents that claimed cDNA molecules in combination with other genetic material. See, *e.g.*, U.S. Patent No. 4,322,499 (filed Mar. 30, 1982). In subsequent years, the PTO began to grant patents directed to isolated DNA.

In 2001, in responding to public comments on proposed revised examination guidelines concerning the "utility" requirement of 35 U.S.C. 101, the PTO issued its only written articulation of its views on isolated DNA patents. See Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001). The PTO stated that if the patent discloses a particular use for a gene—*e.g.*, expressing a useful protein—then "an inventor's discovery of a gene can be the basis for a patent on the genetic composition isolated from its natural state." *Id.* at 1093. The PTO explained that a DNA molecule that has been "isolated" in this way is not a product of nature "because that DNA molecule does not occur in that isolated form in nature." *Ibid.*

4. a. In 2009, petitioners, a group of medical researchers, associations, and patients, filed this action challenging 15 claims drawn from seven United States patents owned by, or exclusively licensed to, respondents.[1] The patents relate to the human genes known as Breast Cancer Susceptibility Genes 1 and 2, or

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[1] Petitioners named the PTO as a defendant with respect to constitutional claims, but not with respect to the statutory claims at issue in this Court. The district court dismissed the claims against the PTO, Pet. App. 355a-357a, and petitioners did not appeal that ruling. The United States participated as amicus curiae in the court of appeals. As in this brief, the United States argued in the Federal Circuit that cDNA is patent-eligible but that isolated DNA is not.

"BRCA1" and "BRCA2."[2] See generally Pet. App. 297a-310a. Mutations in these genes are associated with significantly increased risks of breast and ovarian cancer. *Id.* at 379a-380a.

Several of the composition claims in the patents-in-suit, including claim 2 of the '282 patent, are limited to cDNAs that encode the BRCA proteins. See Pet. App. 426a. Other claims at issue would encompass isolated but otherwise unmodified human genomic DNA. For instance, claim 1 of the '282 patent claims "[a]n isolated DNA coding for a BRCA1 polypeptide," or protein, "said polypeptide having the amino acid sequence set forth in SEQ ID NO:2." *Id.* at 298a. "SEQ ID NO:2" describes the amino-acid sequence of the BRCA1 protein as it occurs in nature. See J.A. 755 (col. 19, lines 41-50). The specification defines the term "isolated DNA" to include, as relevant here, both cDNAs and genomic DNA that has been "separated from other cellular components which naturally accompany a native human sequence" and "removed from its naturally occurring environment." *Ibid.* (col. 19, lines 8-18). Accordingly, claim 1 of the '282 patent encompasses any isolated DNA molecule that codes for the natural BRCA1 protein—including an ordinary BRCA gene isolated from a tissue sample taken from any patient.

b. The district court held that petitioners had standing to challenge respondents' patents, Pet. App. 392a-412a; that all of the challenged composition claims were invalid because they were directed to patent-ineligible products of nature, *id.* at 232a-357a; and that the challenged method claims were also invalid, *id.* at 344a-355a.

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[2] The United States is a co-owner of four of the patents-in-suit. Pet. App. 377a n.4. In 1995, the government granted an exclusive license under those patents to respondent Myriad.

5. a. A divided panel of the Federal Circuit reversed in relevant part and remanded. Pet. App. 120a-231a. The court of appeals unanimously held that the district court had declaratory-judgment jurisdiction because "at least one" petitioner, Dr. Ostrer, had standing. *Id.* at 9a, 28a-41a, 148a-158a. The court unanimously held that cDNA molecules are patent-eligible. *Id.* at 169a, 192a-193a, 225a. A majority of the panel also concluded that isolated DNA is patent-eligible. *Id.* at 159a-172a; *id.* at 193a-212a (Moore, J., concurring).[3]

b. Petitioners filed a petition for a writ of certiorari (No. 11-725). While that petition was pending, this Court issued its decision in *Mayo*, *supra*. *Mayo* concerned diagnostic method claims that "purport[ed] to apply" what this Court characterized as "natural laws describing the relationships between" the blood concentration of certain metabolites and appropriate drug dosage. 132 S. Ct. at 1294. This Court held that the method claims were invalid because they did not contain elements "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself." *Ibid.* The Court then granted the petition in No. 11-725, vacated the court of appeals' judgment, and remanded for further proceedings in light of *Mayo*. *Id.* at 1794.

6. On remand, the same panel reaffirmed its earlier conclusions, principally for the same reasons it had previously given. Pet. App. 1a-119a. The court held that certain of the challenged claims were limited to cDNA molecules, and that such molecules are patent-eligible because they are synthesized by scientists. *Id.* at 47a n.9, 54a, 80a-81a, 113a-114a. Judges Lourie and

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[3] The court of appeals also held that all but one of respondents' method claims were invalid. Pet. App. 62a-70a, 172a-179a.

Moore concluded that isolated DNA is patent-eligible, each offering different reasons for that conclusion. Judge Bryson dissented from that holding.

Judge Lourie reasoned that isolated genes "are markedly different—have a distinctive chemical structure and identity—from those found in nature." Pet. App. 50a-51a. He explained that separating DNA from the human body entails breaking chemical bonds, and that the separated "portion [of DNA] never exists as a separate molecule in the body or anywhere else in nature, and may have an entirely different utility." *Id.* at 57a. Judge Lourie also invoked the "longstanding practice of the PTO," noting that "Congress has not indicated that the PTO's position is inconsistent with [Section] 101." *Id.* at 62a.

Judge Moore did not join Judge Lourie's opinion with respect to isolated DNA, but instead concurred in the judgment. Pet. App. 73a-96a. In her view, isolated DNA could be patent-eligible only if, in addition to the chemical differences highlighted by Judge Lourie, isolated DNA had greater utility than native DNA. *Id.* at 82a-83a. She concluded that shorter isolated DNA segments had the necessary additional utility because they could be used as primers and probes. *Id.* at 83a-84a. Judge Moore viewed "longer strands of isolated DNA" as presenting a closer question because those strands do not clearly involve increased utility "as compared to nature." *Id.* at 85a-86a. She ultimately concluded, however, that the court should not disturb the "settled expectations" and "extensive property rights" engendered by the PTO's practice of allowing patents on such sequences. *Id.* at 86a.

Judge Bryson dissented, concluding that isolated DNA is not patent-eligible. Pet. App. 98a-119a. In his view, *Mayo* suggested that "[i]n cases such as this one, in which the applicant claims a composition of matter that is nearly identical to a product of nature, it is appropriate to ask whether the applicant has done 'enough' to distinguish his alleged invention from the similar product of nature." *Id.* at 112a. Judge Bryson would have held that isolated DNA did not satisfy that standard because "[t]he only material change made to those genes from their natural state is the change that is necessarily incidental to the extraction of the genes from the environment in which they are found in nature." *Id.* at 102a. Judge Bryson also disagreed with the majority's reliance on the PTO's practice of issuing isolated DNA patents and the "expectations of the inventing community." *Id.* at 119a. He explained that such considerations could not override the rule against patenting products of nature. *Ibid.*

SUMMARY OF ARGUMENT

Synthesized genetic materials such as cDNA are patent-eligible subject matter because they do not occur in nature but instead are the product of significant human creativity. By contrast, isolated but otherwise unmodified DNA is not patent-eligible. The public's ability to study and use native DNA would be unduly compromised if changes caused by the extraction of naturally-occurring substances from their native environments were sufficient to trigger patent-eligibility. And while the process of isolating DNA entails physical changes, those changes do not significantly alter the structure or function of the relevant DNA segments.

A. Under this Court's longstanding precedents, laws and products of nature cannot be patented. That is so even if significant effort and creativity are required to discover the natural law or substance and to appreciate its potential utility. A patent may be issued for a modified natural substance if the modified version is sufficiently different from its naturally occurring antecedent and the other statutory requirements for patentability are satisfied. In deciding whether a particular modified substance is patent-eligible under these standards, a court should ask, *inter alia*, whether issuance of a patent would have the practical effect of preempting all use of the underlying natural substance.

B. Artificial DNA molecules such as cDNAs are patent-eligible inventions. Creating cDNA requires significant manipulation and alteration of naturally occurring genetic materials rather than simply the extraction of those materials from their native environment. Issuing patents on cDNA creates no risk of preempting other uses of the raw materials from which cDNA is created.

C. Isolated but otherwise unmodified genomic DNA is not patent-eligible. In their naturally occurring state—*i.e.*, as a portion of a larger native strand within a cell, which in turn is located within the human body—the DNA molecules claimed in respondents' patents are products of nature. The process of isolation does not transform those molecules into human-made inventions.

As with many naturally occurring substances, the process of "isolating" a particular DNA segment changes the molecule's physical structure to a degree (since the ends of the segment must be "snipped" in order to remove it from the cell of which it is a part) and increases its utility (since isolation allows researchers to study and exploit it in a laboratory). Those changes, however, are simply inherent consequences of removing the original substance from its natural environment. Since isolation is a prerequisite to meaningful productive use of native DNA, treating such changes as sufficient to support patent-eligibility would effectively preempt the public's use of the underlying product of nature.

Congress's failure to amend the Patent Act to foreclose the patenting of isolated DNA does not imply congressional approval of such patents. Since the 1980s, the PTO has issued patents on both isolated DNA and cDNA. It was not until 2001, however, that the PTO issued its first written explanation of its view that isolated DNA is patent-eligible, and that view was not tested in court until this litigation commenced. This case is therefore unlike prior patent-law disputes where the Court has given weight to reliance interests engendered by established judicially-created doctrines.

The court of appeals also suggested that factors specific to the biotechnology industry supported a narrow view of the product-of-nature exception to patent-eligibility. This Court has eschewed that sort of industry-specific approach to patent-eligibility, preferring instead to establish general rules designed to strike an appropriate balance between competing objectives. One such rule is that patents may not be issued on products of nature, even though such products may benefit the public, and even though the availability of patents would increase the incentives for researchers to discover such substances and ascertain their useful properties. The determination whether such rules should be modified in their application to particular industries or categories of inventions has traditionally been left to Congress. And the product-of-nature exception itself serves important public purposes (including incentives for innovation), since an overbroad conception of patent-eligibility could unduly restrict the public's study and productive use of resources found in the natural world.

ARGUMENT

SYNTHESIZED GENETIC MATERIALS SUCH AS cDNA MOLECULES ARE PATENT-ELIGIBLE SUBJECT MATTER, WHILE ISOLATED BUT OTHERWISE UNMODIFIED GENOMIC DNA IS NOT

Petitioners contend that respondents' claims to cDNA molecules and to isolated but otherwise unmodified DNA are directed to patent-ineligible products of nature. In the government's view, cDNA is patent-eligible under Section 101 because it must be synthesized from other genetic materials, a process that involves significant manipulation and leaves the public free to exploit the underlying natural substances used to create cDNA. Isolated DNA, by contrast, is not patent-eligible because it has merely been "isolated"—*i.e.*, extracted from its cellular environment and separated from extraneous material—rather than significantly altered by human intervention. Because the differences between isolated and native DNA are simply the necessary consequences of removing DNA from its natural environment, and DNA must be isolated before it can be exploited, respondents' isolated DNA claims threaten to preempt the use of the underlying native DNA. See *Mayo Collaborative Servs.* v. *Prometheus Labs.*, 132 S. Ct. 1289, 1294 (2012). To prevent that result, the mere act of culling a natural product from its environment to exploit its preexisting natural qualities—however useful those qualities may be—should be treated as insufficient to create patent-eligible subject matter.

The PTO has regularly issued patents directed to isolated genomic DNA, and various government agencies have previously sought and obtained such patents. The patent-eligibility of isolated DNA was never tested in litigation, however, until petitioners filed this suit. Before the district court, the government, in the course of defending against petitioners' constitutional claims, stated that "the USPTO's position" on whether "DNA molecules" are patent-eligible "remains as set forth in its Utility Guidelines." PTO Reply Br. at 11, Docket entry No. 245, 09-cv-4515 (Jan. 29, 2010). The district court's judgment in this case, however, prompted the United States to reevaluate whether such patents are consistent with the settled principle that patent protection does not extend to products of nature. Based on that review, the United States concluded that, although the PTO has properly issued patents on cDNA and other synthesized genetic materials, isolated DNA is not patent-eligible subject matter.[4]

A. Section 101 Embraces Only "Human-Made Inventions" That Do Not Monopolize Laws Or Products Of Nature

1. Section 101 of Title 35 broadly permits an inventor to obtain a patent on "any new and useful process, machine, manufacture, or composition of matter." 35 U.S.C. 101. "[A]s a matter of statutory *stare decisis* going back 150 years," however, the provision's scope has been limited by an implicit exception under which "[l]aws of nature, natural phenomena, and abstract ideas" are not patentable. *Bilski* v. *Kappos*, 130 S. Ct. 3218, 3225 (2010); *Mayo*, 132 S. Ct. at 1293. Such manifestations of nature are "free to all men and reserved exclusively to none." *Diamond* v. *Chakrabarty*, 447 U.S.

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[4] The court of appeals correctly held that the district court had jurisdiction to adjudicate petitioners' claims. Pet. App. 25a, 32a-41a. Dr. Ostrer has standing to challenge the validity of respondents' patents because his research activities are constrained by respondents' assertion of their rights under allegedly invalid patents. See *Already, LLC* v. *Nike*, No. 11-982 (Jan. 9, 2013), slip op. 5; *MedImmune, Inc.* v. *Genentech, Inc.*, 549 U. S. 118, 126-137 (2007).

303, 309 (1980) (citation omitted). Thus, "a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter," even though the discovery and acquisition of the mineral or plant, and the identification of its useful properties, may have required significant effort and ingenuity. *Ibid.*; see, *e.g.*, *Diamond* v. *Diehr*, 450 U.S. 175, 185-186 (1981).

The Court has recognized, however, that "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas." *Mayo*, 132 S. Ct. at 1293. While one cannot patent a "new plant found in the wild," *Chakrabarty*, 447 U.S. at 309, modifications of plant substances found in nature, as well as new plants bred from existing ones, may be patent-eligible. See *J.E.M. Ag Supply Inc.* v. *Pioneer Hi-bred Int'l, Inc.*, 534 U.S. 124, 130-131, 134 (2001) (*J.E.M. Ag Supply*). The patent-eligibility of a modified natural substance depends on whether the modified substance is so "markedly" different from its natural predecessor as to warrant the conclusion that the claimant has invented something new. *Chakrabarty*, 447 U.S. at 309-310; cf. *Mayo*, 132 S. Ct. at 1302 (process claim that "add[ed] nothing of significance to the natural laws themselves" was invalid).

2. This Court has twice considered whether a substance derived from nature falls within the product-of-nature exception to Section 101. In *Chakrabarty*, the Court held that a genetically engineered microorganism useful for digesting oil spills was patent-eligible because it had "*markedly different* characteristics from any found in nature and [had] the potential for significant utility." 447 U.S. at 309-310 (emphasis added). The inventor had altered a naturally occurring bacterium by transferring to it several plasmids that altered the bac-

terium's structure and imbued it with the ability to break down crude oil—a "property[] which [was] possessed by no naturally occurring bacteria." *Id.* at 305. It was the "markedly different" characteristics of the modified substance that made it useful. The Court therefore concluded that the patentee's "discovery is not nature's handiwork, but his own; accordingly it is patentable subject matter under [Section] 101." *Id.* at 310.

By contrast, in *Funk Brothers Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127 (1948), the Court held that natural strains of root-nodule bacteria were not patent-eligible. The patentee had "discovered that there existed in nature certain species of root-nodule bacteria which did not exert a mutually inhibitive effect on each other." *Chakrabarty*, 447 U.S. at 310. He accordingly created a mixed culture containing several such species, which could be used to inoculate the seeds of several different types of plants at once. *Ibid.*; see *Funk Brothers*, 333 U.S. at 130. The Court emphasized that, although the patentee had discovered the bacteria strains' natural properties, he had not altered the bacteria in any way. *Id.* at 131. In addition, although the bacteria within the mixed culture had applications that single strains did not—in that the culture could be used to inoculate multiple types of plants at once—the Court emphasized that, within the culture, the unaltered "bacteria perform[ed] in their natural way." *Ibid.*

Chakrabarty and *Funk Brothers* thus establish that, although an inventor may not obtain a patent merely by discovering the existence or useful properties of a natural substance, patents may be issued on new substances created out of naturally occurring raw materials. *Chakrabarty*, 447 U.S. at 310; *Funk Brothers*, 333 U.S. at 131. Since *Chakrabarty*, however, the Court has not had occasion to further elaborate on the nature or extent of the modifications that may be sufficient to warrant the conclusion that a substance derived from a natural product is sufficiently different from nature to be considered a man-made invention.

3. Although this Court's decision in *Mayo* concerned process rather than composition claims, it provides useful guidance for determining whether particular modifications to a naturally occurring substance are sufficient to render the modified substance patent-eligible.

In *Mayo*, the Court addressed a therapeutic method patent based on the correlation between patient metabolite levels after administering a drug and the likely safety and efficacy of that drug. 132 S. Ct. at 1294. The Court held that the patent was invalid because the correlation was a law of nature and the patent posed a risk of "disproportionately tying up" its future uses. *Ibid.* The Court explained that the "basic underlying concern" of the natural-law exception to Section 101 is that patentees must not be allowed, through "drafting effort[s]," to "monopolize the law of nature itself." *Id.* at 1297, 1302. When a claimed process is centered on a natural law, the method as a whole therefore must "contain other elements * * * sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself." *Id.* at 1294; see, *e.g.*, *id.* at 1301.

Not every nuance of *Mayo*'s process-claim analysis applies directly to patents directed to compositions of matter. The law-of-nature and product-of-nature exceptions to Section 101 do, however, reflect the same basic principle: a person should not receive a patent for simply discovering the existence and useful properties of something that already exists in nature. See *Chakrabarty*, 447 U.S. at 309 (both plants in the wild and mathematical laws are "manifestations of . . . nature") (citation omitted). A composition claim that effectively prevents the public from studying and using a *product* of nature is just as objectionable as a method claim that prevents the public from studying and exploiting a *law* of nature.

Mayo thus suggests that, in determining whether a modified natural product is "markedly different" from the underlying natural substance and therefore patent-eligible, one relevant question is whether a patent on the modified product would have the practical effect of preempting the public's ability to use the underlying natural substance. If so, then the differences between the claimed invention and the underlying natural substance are not sufficient to render the composition patent-eligible. See 132 S. Ct. at 1294. This inquiry into preemptive effect is not an exclusive test of the patent-eligibility of a product derived from nature. The patent at issue in *Funk Brothers*, 333 U.S. at 130, for example, was held invalid even though it would not have prevented exploitation of any single strain of bacteria. But *Mayo* indicates that, at a minimum, a substance derived from a product of nature should not be considered patent-eligible if the patent would have the effect of preempting all uses of the underlying natural substance.

In particular, extending patent eligibility to a modified natural substance may risk "tying up" the underlying natural substance when the differences between the modified and original substances consist of nothing more than the necessary consequences of removing the substance from its natural environment. Removing a product of nature from its natural surroundings is often a prerequisite to any serious study or commercial exploitation of that product. When that is so, and the act of removal would necessarily result in the creation of a patented composition, the patent risks preempting all future uses of the natural product. It therefore does not "in practice amount[] to significantly more than a patent on the natural [product] itself." *Mayo*, 132 S. Ct. at 1294.

B. Artificial DNA Molecules, Including cDNAs, Are Human-Made Inventions Eligible For Patent Protection

cDNA molecules are synthesized nucleotide sequences that contain only the exons of a naturally occurring gene. With exceptions not relevant here (such as retroviruses that use cDNA-like structures to replicate themselves), cDNA molecules generally do not occur in nature, either in isolation or as contiguous sequences contained within longer natural molecules. Pet. App. 268a. To create cDNA, a scientist therefore does not simply remove existing cDNA from its natural environment. Rather, scientists must synthesize cDNA from other genetic materials, a process that involves significant manipulation of the underlying natural substances to create a substance that is new and different. See p. 4, *supra*. The resulting cDNA molecule has a different nucleotide sequence than DNA created naturally within the cell, and (because it lacks introns) it is "preferable" to isolated DNA for many laboratory uses. See Bruce Alberts et al., *Molecular Biology of the Cell* 504 (Garland Science 4th ed. 2002).

Extending patent protection to cDNAs therefore poses no risk of "tying up" other uses of the natural raw materials involved in the creation of cDNA. *Mayo*, 132

S. Ct. at 1294. A patent on a particular cDNA molecule leaves others free to study and exploit the original native DNA, RNA, and mRNA molecules that were used to create the cDNA. Those substances can be removed from their cellular environment and studied without creating the patented cDNA molecule, and they can be altered in ways that do not result in the creation of the cDNA. cDNA is thus analogous to the genetically modified bacterium in *Chakrabarty*. Upholding the patent on that bacterium did not prevent others from investigating or experimenting upon the original, naturally occurring micro-organism. See 447 U.S. at 310.

Petitioners contend (Br. 49-53) that cDNAs are not patent-eligible because they contain the same protein-coding information—*i.e.*, exon sequences—as DNA in the body. But the properties of any product originally derived from nature, including the bacterium in *Chakrabarty*, can be traced to the operation of natural principles. While the coding properties of cDNA molecules' exons are determined by nature, those properties operate within a molecule (a DNA strand with the regulatory and intron regions spliced out) that does not exist in nature and that has increased utility relative to naturally occurring genetic materials or isolated but unmodified DNA. The fact that a cDNA incorporates nucleotide sequences whose significance is derived from nature therefore does not mean that the molecule as a whole is a product of nature.[5] See *Diehr*, 450 U.S. at 187.

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[5] It is possible that, given the prevailing level of knowledge in biotechnological fields, future patent applications directed to cDNAs and other synthesized DNA molecules may be rejected as obvious. 35 U.S.C 103; see *In re Kubin*, 561 F.3d 1351, 1358-1361 (Fed. Cir. 2009).

C. Isolated But Otherwise Unmodified Genomic DNA Is Not Patent-Eligible

Respondents' claims directed to isolated DNA are invalid under Section 101. Isolated DNA is simply naturally occurring DNA that has been extracted from its cellular environment and separated from extraneous material. The differences between isolated DNA and native DNA within a cell are merely the inherent and necessary results of removing the DNA from its natural environment. Because the removal process is a prerequisite to any exploitation of native DNA, respondents' isolated DNA claims are the practical equivalent of patents on the underlying naturally occurring BRCA genes themselves.

1. Isolated DNA is not markedly different from native DNA

a. Respondents' composition claims are directed to "isolated" DNA molecules that have been extracted from their natural cellular environment and excised from other portions of the gene. Absent the "isolated" limitation, claim 1 of the '282 patent, for example, would encompass the native BRCA1 gene in the human body, which "cod[es] for a BRCA1 polypeptide."[6] Pet. App. 426a. In their pre-isolation form—*i.e.*, as a portion of a larger native gene within a cell—the BRCA sequences clearly are products of nature. Independent of any human intervention, BRCA genes exist within the human genome and, together with the rest of the genome and other materials, are packaged into chromosomes within each cell. *Id.* at 262a. Also independent of human intervention, the unique nucleotide sequence of BRCA genes induces human cells to express the BRCA1 protein, and certain mutations in that sequence are associated with an increased risk of cancer.

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[6] Several of the disputed claims, including claim 1 of the '282 patent, are framed in functional terms that would additionally encompass non-naturally occurring variations of the BRCA genes and related cDNAs. But because the challenged claims in respondents' patents encompass the isolated natural gene as well, they are invalid under Section 101. See *Titanium Metals Corp.* v. *Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985).

As the court of appeals recognized, the process of excising a selected portion of DNA from its cellular environment results in a molecule that is distinct from native DNA in certain respects. Pet. App. 51a-52a; see *id.* at 308a-309a. The isolated DNA segment is structurally different from native DNA, in that each end of the isolated DNA segment is no longer bonded to the rest of the gene. *Id.* at 51a-52a. Within the isolated DNA segment, however, the nucleotide sequence (which contains both the protein-coding exons and non-coding sequences) is unchanged. *Id.* at 20a.

Although isolated DNA has applications that native DNA does not, that is a consequence of the fact that DNA, once isolated, can be manipulated by scientists in a laboratory. Isolated DNA can be sequenced and analyzed. Shorter isolated strands may also be used, with some modifications, as probes, which are used to target and bind to a particular DNA segment, and primers, which can be used to help determine the order of nucleotides in a DNA molecule. Pet. App. 264a-265a, 269a-270a. All of these applications depend on the fact that isolated DNA's nucleotide sequence is identical to that of the same gene segment as it exists within a cell, so that the isolated DNA binds with the same complementary nucleotide sequences as it would in non-isolated form. *Ibid.*

b. These distinctions between isolated and native DNA do not render isolated DNA "markedly different" from native DNA.

The structural difference between isolated DNA and native DNA—the isolated segment's "snipped" ends—has no functional consequences. That truncation does not alter any of the operative properties of the isolated DNA segment. In particular, the nucleotide sequence that determines the binding and coding properties of a given DNA segment is exactly the same after the segment has been isolated as it was when it existed as part of the genome in the human body. Judge Lourie viewed the fact that "[i]solated DNA has been cleaved (*i.e.*, had covalent bonds in its backbone chemically severed)" as sufficient to render isolated DNA patent-eligible. Pet. App. 51a, 53a-54a. But if a structural change that leaves the natural substance's operative properties entirely untouched were sufficient in itself to support patent-eligibility, the removal of a kidney from the body might render the extracted kidney patent-eligible.[7] *Id.* at 107a (Bryson, J., dissenting).

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[7] Judge Lourie emphasized that the distinct structure of isolated DNA manifests itself at the molecular level. Pet. App. 51a-52a, 54a-55a, 57a. But there is no sound reason that "it should make a difference, for purposes of patentability, whether the isolated substance is part of a single molecule * * * or part of a very large aggregation of molecules, as in the case of a kidney." *Id.* at 107a (Bryson, J., dissenting); cf. *Mayo*, 132 S. Ct. at 1303 (refusing to distinguish between narrow and broad natural laws for patent-eligibility purposes). Judge Lourie also concluded that isolated DNA, unlike an extracted kidney, warrants patent protection because isolating DNA requires "extensive research" and skill. Pet. App. 60a. That reasoning conflates the patent-eligibility of the extraction method with that of the resulting isolated substance. The process of extracting a segment of DNA (now well understood in the art) was undoubtedly patent-

The fact that isolated DNA has additional applications likewise does not render it markedly different from native DNA. The "additional utility" on which the concurring judge below relied (Pet. App. 82a-84a) is simply the ability of researchers to study and exploit in a laboratory the inherent natural properties that isolated DNA shares with native DNA. For two of the composition claims at issue here, the relevant compositions of matter are defined by the natural biological function they perform in the human body: the capacity to express BRCA1 and BRCA2 proteins. See *id.* at 426a-427a.

Indeed, the isolated gene is important to respondents and the medical community precisely because isolated DNA operates in exactly the same way in a laboratory as it does in its natural environment. Thus, human manipulation has resulted only in an increased ability to exploit the DNA segment's natural properties, rather than in increased utility arising from altered properties. In this respect as well, isolated DNA is analogous to a kidney removed from the body or a plant obtained from the wild, and is unlike the modified bacterium in *Chakrabarty*, which had additional utility arising from the non-natural properties created by human intervention.

These differences between isolated and native DNA cannot render isolated DNA patent-eligible. "The only material change made to [isolated] genes from their natural state is the change that is necessarily incidental to the extraction of the genes from the environment in which they are found in nature." Pet. App. 102a

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eligible when it was first conceived. But the effort required to discover or obtain a naturally occurring substance does not make that substance patent-eligible. See *Funk Brothers*, 333 U.S. at 131.

(Bryson, J., dissenting). That isolation process is generally a prerequisite to any serious study or exploitation of the underlying native DNA.[8] See, *e.g.*, *Principles and Techniques of Biochemistry and Molecular Biology* 164 (Keith Wilson & John Walker, eds., 7th ed. 2010); Burton E. Tropp, *Molecular Biology: Genes to Proteins* 151-152 (4th ed. 2012). Many "future use[s]" of native BRCA DNA segments therefore may infringe respondents' patents.[9] *Mayo*, 132 S. Ct. at 1302. By claiming the substance that necessarily results from removing DNA from its cellular environment—the first, necessary step in studying or further exploiting the DNA—respondents' isolated DNA claims "risk disproportionately tying up the use of the underlying natural" products. *Id.* at 1294. Respondents' claimed isolated DNA therefore is not "markedly different" from native DNA, and respondents' isolated DNA claims are invalid. *Chakrabarty*, 447 U.S. at 310.

The need to "isolate" a natural substance in order to study or exploit it is hardly unique to DNA. Many natural products—coal beneath the earth, cotton fibers mixed with cotton seeds, the stigmas of the saffron flower—must be physically separated, *i.e.*, "isolated," from their environments before becoming useful to mankind. Similarly, many highly reactive elements on the periodic table, such as lithium, boron, and barium, occur in nature only in chemical compounds. The isolation of lithium and other elemental metals marked significant scientific achievements. Under Section 101 and its statutory predecessors, however, the isolation of such substances from their natural environments has not been viewed as the "invention" of a new patent-eligible "manufacture" or "composition of matter." Indeed, courts in the early part of the 20th century repeatedly rejected claims for isolated natural elements as new "manufacture[s]."[10] See, *e.g.*, *General Elec. Co.* v. *De Forest Radio Co.*, 28 F.2d 641, 642-643 (3d Cir. 1928), cert. denied, 278 U.S. 656 (1929); *In re Marden*, 47 F.2d 957 (C.C.P.A. 1931).

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[8] DNA sequencing technologies rely on first isolating and breaking down DNA into segments shorter than—and thus potentially contained within—the claimed BRCA segments. See, *e.g.*, Thomas Kepler et al., *Metastasizing patent claims on BRCA1*, 95 Genomics 312-314 (2010).

[9] Anyone who isolates either BRCA gene, or any fragment thereof that is at least 15 nucleotides long, would infringe one or more of respondents' claims. See Pet. App. 426a.

c. Respondents have argued (Resps. C.A. Br. 36-40), and the concurring judge below agreed (Pet. App. 76a-78a), that isolated DNA is patent-eligible as a "purified" natural substance. They rely on early lower-court decisions upholding patents on natural compounds that have been so refined and purified through human intervention as to become a substance different "in kind" from the natural product. See, *e.g.*, *Kuehmsted* v. *Farbenfabriken of Elberfeld Co.*, 179 F. 701 (7th Cir. 1910) (purified aspirin had "therapeutically different" properties from impure substance), cert. denied, 220 U.S. 622 (1911); *Parke-Davis & Co.* v. *H.K. Mulford Co.*, 189 F. 95, 103 (S.D.N.Y. 1911), aff'd in part and rev'd in part, 196 F. 496 (2d Cir. 1912); see also *In re Merz*, 97 F.2d 599 (C.C.P.A. 1938).

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[10] The court of appeals viewed isolated elements as distinguishable from isolated DNA because isolated elements reflect "a simple separation from extraneous materials," Pet. App. 59a, and represent "basic building block[s] provided by nature," *id.* at 90a n.7 (Moore, J., concurring). But the isolation of elements, like the isolation of DNA, merely reflects the modifications inherent in removing the relevant natural substance from its environment. In neither context does the fact of isolation create a new patent-eligible substance.

Those decisions indicate that certain purification processes—*i.e.*, processes that involve human manipulation of a substance that has been removed in impure form from its natural environment—may sometimes result in an altered substance that has structural features and/or operative properties that render the product markedly different from the impure substance that occurs in nature. For instance, cDNA could be thought of as a "purified" gene, as it incorporates into a single contiguous, synthetic molecule only the coding regions of the naturally occurring gene. But isolated DNA reflects no such transformation. As explained above, isolated DNA has simply been removed from its natural environment within the human body, with minor structural changes that have no effect on its intrinsic properties, so that those properties may be observed and exploited in a laboratory setting. To label the process of removing DNA from a cell "purification," and to hold the culled DNA segments patent-eligible on that ground, would "make patent eligibility depend simply on the draftsman's art," without reference to the nature and extent of the underlying transformation, or the consequences for the public's ability to use the underlying substance. See *Mayo*, 132 S. Ct. at 1294 (citation and internal quotation marks omitted).

2. Neither the PTO's practice of issuing patents for isolated DNA, nor Congress's failure to overturn that practice, provides a sufficient reason to hold that isolated DNA is patent-eligible

a. Respondents argued below, and the concurring judge agreed, that Congress's failure to amend the Patent Act implies congressional endorsement of the

PTO's practice of granting patents for isolated DNA molecules. Pet. App. 86a-94a (Moore, J., concurring). Since the 1980s, the PTO has issued patents on isolated DNA, as well as on patent-eligible genetic materials such as cDNAs.[11] *Id.* at 87a-88a. As a general matter, however, the agency has historically viewed isolation standing alone as an insufficient basis for finding modified natural substances to be patent-eligible. See, *e.g.*, *Ex parte Latimer*, 1889 Dec. Comm'r Patent 123, 127 (1889) (fiber extracted from pine-tree needles "can no more be the subject of a patent in its natural state when freed from its surroundings than wheat which has been cut by a reaper"); see also *Ex parte Berkman*, 90 U.S.P.Q. 398, 401 (1951).

After the Federal Circuit's predecessor court issued decisions that could be read to support the patent-eligibility of natural substances removed from their environment, see *In re Bergstrom*, 427 F.2d 1394, 1401 (C.C.P.A. 1970); *In re Bergy*, 596 F.2d 952 (C.C.P.A. 1979), vacated in part, 444 U.S. 1028 (1980), and this Court held the modified organism in *Chakrabarty* to be patent-eligible, the PTO began to issue patents on isolated DNA. In 2001, the PTO issued its first written explanation of that practice. In response to comments concerning proposed revisions to its Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001), the PTO stated that an isolated DNA molecule is not a product of nature "because that DNA molecule does not occur in that isolated form in nature." *Id.* at 1093. The PTO's revised Utility Examination Guidelines themselves did not have the force of law, *id.* at 1098, and they did not specifically address patents on DNA. The purpose of soliciting public comments, moreover, was not to consider whether to begin granting isolated DNA patents, or even to consider whether to continue that practice, but instead to consider the standard for determining utility generally. See 64 Fed. Reg. 71,441 (Dec. 21, 1999).

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[11] Given the different terminology used in different patents, it is difficult to estimate the number of patents issued for isolated DNA. The court of appeals stated that approximately 2645 "patents claiming 'isolated DNA'" have been issued. Pet. App. 61a-62a. There are many thousands of patents on cDNAs and other synthetic materials. *Ibid.*

b. In these circumstances, Congress's failure to enact legislation abrogating the PTO's practice of issuing isolated DNA patents does not give rise to any inference of congressional endorsement of the PTO's interpretation. Unlike in *J.E.M. Ag Supply*, in which this Court inferred that Congress had approved the PTO's practice of granting plant utility patents, here the PTO did not begin issuing isolated DNA patents after any "highly visible" formal administrative action that thoroughly explained the agency's interpretation of the statute. 534 U.S. at 145. And because the correctness of the PTO's practice was never challenged in litigation prior to this case, there was no extant judicial decision applying Section 101 to isolated DNA patents.

Moreover, although bills relating to patents on genetic materials have occasionally been introduced in Congress, there is little "evidence that Congress considered * * * the *precise* issue presented before the Court." *Rapanos* v. *United States*, 547 U.S. 715, 750 (2006) (plurality opinion) (citation omitted). Most of the proposed bills addressed the general policy implications of patents on all types of genetic materials, including synthesized materials. See Genomic Science and Technology Innovation Act of 2002, H.R. 3966, 107th Cong., 2d Sess. (2002); Genomic Research and Diagnostic Accessibility

Act of 2002, H.R. 3967, 107th Cong., 2d Sess. (2002); Life Patenting Moratorium Act of 1993, S. 387, 103d Cong., 1st Sess. (1993); see also Consolidated Appropriations Act, 2004, Pub. L. No. 108-199, § 634, 118 Stat. 101 (prohibiting use of funds to issue patents on "human organism[s]"). Although one bill would have prohibited patents on "nucleotide sequence[s]," it was never brought to a vote, and its application to isolated DNA molecules (as opposed to the information contained in nucleotide sequences) is not clear from its text. See Genomic Research and Accessibility Act, H.R. 977, 110th Cong., 1st Sess. (2007). Because "Congress takes no governmental action except by legislation," and bills can be proposed and rejected for any number of reasons, none of these bills raises any inference that Congress approved the PTO's practice of granting patents on isolated DNA. *Rapanos*, 547 U.S. at 750; *Solid Waste Agency* v. *U.S. Army Corps of Eng'rs*, 531 U.S. 159, 169-170 (2001); cf. *J.E.M. Ag Supply*, 534 U.S. at 145 (relying on Congress's enactment of legislation reflecting the premise that plants could be patented).

c. The court of appeals' decision also reflected the related concern that invalidating patents on isolated DNA would unduly disturb the "settled expectations" of biotechnology patent holders and investors. See Pet. App. 61a-62a (citation omitted); *id.* at 88a (Moore, J., concurring). The patent laws are designed to promote the development of new and useful inventions, and to encourage the dissemination of knowledge that enables others to replicate those inventions, by offering as a reward a promise of exclusivity to those who satisfy the statutory requirements. The PTO's known practice of issuing patents for isolated DNA molecules therefore could reasonably be expected to increase the incentives for genomic research.

A patentee's legitimate expectations, however, are always tempered by the possibility that a court could subsequently disagree with the PTO and hold that the patent is invalid under Section 101 or other provisions of the Patent Act. See, *e.g.*, *Mayo*, 132 S. Ct. at 1304-1305 (invalidating diagnostic-method patent despite industry's reliance interests); Pet. App. 119a (Bryson, J., dissenting) ("There is no collective right of adverse possession to intellectual property."). And while the PTO's practice of issuing patents for isolated DNA is relatively longstanding, no court had ever specifically upheld the patent-eligibility of isolated DNA until the court of appeals ruled in this case. The reliance interests at stake here therefore are not comparable to those to which the Court gave weight in *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002), and *Warner-Jenkinson Co.* v. *Hilton Davis Chemical Co.*, 520 U.S. 17, 41 (1997) (Ginsburg, J., concurring), in which the Court considered the scope and contours of the judicially-created principles of prosecution-history estoppel and the doctrine of equivalents. In those cases, the "settled expectations of the inventing community" were entitled to particular solicitude because those expectations arose from the longstanding judicial decisions that had initially created the relevant doctrines. See *Festo*, 535 U.S. at 739. Reversal of the court of appeals' judgment with respect to isolated DNA would not disturb any analogous body of judicial precedent.

3. *Field-specific concerns about encouraging innovation do not justify treating isolated DNA as patent-eligible*

The court of appeals' holding that isolated DNA is patent-eligible rested in part on the court's desire to avoid the "adverse effects on innovation that a holding of ineligibility might cause." Pet. App. 62a; *id.* at 60a-61a; *id.* at 95a (Moore, J., concurring). But although encouraging innovation is an underlying purpose of the patent system, the desire to encourage innovation in a particular field cannot render patent-eligible products that are not the result of human invention. The prospect of patent protection for isolated genomic DNA has undoubtedly encouraged valuable discoveries. By the same token, however, patent protection would create additional incentives to discover many difficult-to-obtain but clearly patent-ineligible products of nature, such as previously unknown mineral ores or plants growing in the wild. Cf. *Funk Brothers*, 333 U.S. at 130. As this Court explained in *Mayo*, natural phenomena are not patentable "even though rewarding with patents those who discover new laws of nature and the like might well encourage their discovery." 132 S. Ct. at 1301.

The court of appeals suggested that the product-of-nature exception to Section 101 should be given a particularly narrow construction in the biotechnology context because "the biotechnology industry * * * depends on patents to survive." Pet. App. 95a (Moore, J., concurring); see *id.* at 44a, 59a-60a. Biotechnology researchers will have ample freedom to patent their inventions, however, even if isolated DNA is treated as patent-ineligible. As a general matter, when researchers manipulate and alter natural substances to create new products that are not found in nature (as in the creation of cDNA), patent-eligibility depends on the degree to which the purported invention differs from its naturally-occurring antecedent. There is no evident reason to assume that the standard applied to other industries is unsuited to the biotechnology field. And even though isolated but otherwise unmodified DNA segments are not patent-eligible, novel methods of identifying, isolating, and using DNA molecules—and other products of nature—may be patented, as may any new and useful alteration of those molecules through human intervention.

In any event, this Court has traditionally eschewed the sort of industry-specific calculus that the court below appeared to endorse. In *Mayo*, for example, the Court stated that policy arguments about the need for financial incentives in a particular industry are generally not an appropriate consideration in determining the scope of Section 101. See 132 S. Ct. at 1304-1305. This Court's analysis of patent-eligibility under Section 101 reflects an effort to strike an overall balance between encouraging innovation through the promise of exclusivity and preventing unduly broad and preemptive monopolies. See *id.* at 1294, 1305. Because the "general rules" that result from that balancing "must govern inventive activity in many different fields of human endeavor, * * * the practical effects of rules that reflect a general effort to balance these considerations may differ from one field to another." *Id.* at 1305. While "recogniz[ing] the role of Congress in "crafting more finely tailored rules where necessary," the Court has therefore "hesitate[d] before departing from established general legal rules lest a new protective rule that seems to suit the needs of one field produce unforeseen results in another." *Ibid.*

Although the incentives created by the patent laws have spawned enormous public benefits, the product-of-nature exception serves important public purposes as well. The judicially-created exceptions to Section 101 reflect this Court's understanding that "[p]atent protection is, after all, a two-edged sword." *Mayo*, 132 S. Ct. at 1305. The promise of exclusivity that can foster innovation can also "impede the flow of information that might permit, indeed spur, invention," by "raising the price of using * * * patented" products or preventing others from using them at all. *Ibid.* In particular, an overbroad conception of patent-eligibility under Section 101 can impose significant social costs by requiring the public to pay to study and exploit that which ought to be "free to all men and reserved exclusively to none." *Funk Brothers*, 333 U.S. at 130. As between the reliance interests of patent holders whose research efforts may have been prompted in part by the PTO's patenting standards, and the public interest in avoiding undue restrictions imposed by patents that effectively preempt natural laws and substances, the interest of the public has consistently been given precedence. See *Mayo*, 132 S. Ct. at 1294 (Court's precedents "warn us against upholding patents that claim processes that too broadly preempt the use of a natural law"); *Mercoid Corp.* v. *Mid-Continent Inv. Co.*, 320 U.S. 661, 665 (1944) (in the patent system, "the public interest * * * is dominant").

CONCLUSION

The judgment of the court of appeals should be affirmed insofar as it holds that cDNA is patent-eligible, and reversed insofar as it holds that isolated but otherwise unmodified DNA is patent-eligible.

Respectfully submitted.

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JANUARY 2013

AMICUS
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RECORD
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Supreme Court, U.S.
FILED
JAN 31 2013
OFFICE OF THE CLERK

No. 12-398

In The Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,
Petitioners,

v.

MYRIAD GENETICS, INC., ET AL.,
Respondents.

ON WRIT OF CERTIORARI
TO THE UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

BRIEF OF AMICUS CURIAE AARP IN SUPPORT OF PETITIONERS

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INTEREST OF AMICUS CURIAE[1]

AARP is a nonpartisan, nonprofit organization dedicated to addressing the needs and interests of people age fifty and older. AARP seeks through education, advocacy, and service to enhance the quality of life for all by promoting independence, dignity, and purpose. In its efforts to promote independence, AARP works to foster the health and economic security of individuals as they age by attempting to ensure the availability of quality and economical health coverage. AARP has a long history of advocating for access to affordable health care and for controlling costs without compromising quality.

Access to affordable health care is particularly important to the older population, which has higher rates of chronic and serious health conditions. Genetic tests are capable of diagnosing a variety of diseases, assessing the risk of future disease, and enabling treatment to be tailored to individual genetic variations. Patents such as those present in this case significantly elevate the cost of genetic testing, and prohibit diagnosis and treatment based on second medical opinions. In light of the significance of the issue presented in this case, AARP respectfully submits this amicus curiae brief in support of the petitioners.

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[1] In accordance with Supreme Court Rule 37.6, AARP states that: (1) no counsel to a party authored this brief, in whole or in part; and (2) no person or entity, other than AARP, its members and its counsel have made a monetary contribution to the preparation or submission of this brief. Written consent of the parties has been obtained and will be filed with the Clerk of the Court pursuant to Supreme Court Rule 37.3.

SUMMARY OF THE ARGUMENT

Gene patents threaten public health by chilling scientific research and preventing patients from obtaining necessary diagnostic procedures and treatments. Additionally, the monopoly created by gene patents allows the patent holder to charge fees that are unaffordable to many people, effectively denying them life-saving medical treatment.

DNA molecules and human genetic sequences are natural phenomena that, when discovered, are not the kinds of "discover[ies]" that 35 U.S.C. § 101 protects. Gene patents do not promote the progress of science and are not in the public interest.

ARGUMENT

I. Gene Patents Threaten Public Health and Are Not in the Public Interest

The Court has long recognized that "the rights and welfare of the community must be fairly dealt with and effectually guarded" in the patent system. *Kendall v. Winsor*, 62 U.S. (21 How.) 322, 329 (1858). More recently, the Court held that courts must consider the public impact when considering injunctive relief in patent cases. *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 391 (2006).

The ultimate object of the patent laws has always been to benefit, not harm, the public. *See Kendall*, 62 U.S. at 329 ("Considerations of individual emolument can never be permitted to operate to the injury of [the rights and welfare of the community]."). "A patent by its very nature is affected with a public interest. As recognized by the Constitution, it is a special privilege designed to serve the public purpose of promoting the 'Progress of Science and useful Arts.'" *Precision Instrument Mfg. Co. v. Auto. Maint. Mach. Co.*, 324 U.S. 806, 816 (1945) (quoting U.S. Const. art. I, § 8, cl. 8).

A. Gene Patents Have a Chilling Effect on Scientific Research

Unfortunately, gene patents and the omnipresent threat of multi-million dollar patent lawsuits can significantly inhibit genetic research. An example of how gene patents can stymie research—even when defendants succeed in defeating the patents—are the multiple suits brought by the Alzheimer's Institute of America, Inc. ("AIA") concerning research and testing of early onset Alzheimer's Disease. The AIA reportedly purchased a patent from Michael Mullan, a biomedical researcher, who patented a human DNA sequence used in mouse models of early-onset Alzheimer's disease. Erika C. Hayden, *Patent Dispute Threatens US Alzheimer's Research*, 472 Nature 20, 20 (2011), *available at* http://www.nature.com/news/2011/110405/pdf/472020a.pdf. The sequence encodes a mutation which causes early-onset Alzheimer's. *Id.*

The AIA sued private companies, academic institutions, and federally funded laboratories for infringing this patent. *See Alzheimer's Inst. of Am., Inc. v. Avid RadioPharmaceuticals, et al.*, No. 2:10-cv-06908-TJS (E.D. Pa. filed Nov. 24, 2010); *Alzheimer's Inst. of Am., Inc. v. Elan Pharmaceuticals, Inc.*, No. 3:10-cv-00482-EDL (N.D. Cal. filed Feb. 2, 2010); *Alzheimer's Inst. of Am., Inc. v. CoMentis, Inc.*, No. 5:09-cv-01366-F (W.D. Okla. filed Dec. 14, 2009); *Alzheimer's Inst. of Am., Inc. v. Pfizer, Inc.*, No. 4:09-cv-01026-CAS (E.D. Mo. filed June 30, 2009). In the *Avid RadioPharmaceuticals* case, Avid's counsel indicated that Avid incurred over $6.5 million in attorney's fees and $222,000 in costs trying the case, which resulted in a defense verdict. Bill of Costs, *Avid RadioPharmaceuticals, et al.*, No. 2:10-cv-06908-TJS, ECF No.: 318-1; Decl. of L. Scott Burwell, *Avid RadioPharmaceuticals, et al.*, No. 2:10-cv-06908-TJS, ECF No.: 317-4. Even in the AIA cases dismissed before trial, cost bills alone filed by defendants totalled over $130,000, exclusive of attorney's fees. *See* Bill of Costs of Elan, *Elan Pharmaceuticals, Inc.*, No. 3:10-cv-00482-EDL, ECF No.: 323 ($57,555.80); Bill of Costs of Elie Lilly, *Elan Pharmaceuticals, Inc.*, No. 3:10-cv-00482-EDL, ECF No.: 319 ($3,710.59); Bill of Costs, *CoMentis, Inc.*, No. 5:09-cv-01366-F, ECF No.: 182 ($69,482.53). These costs and fees can be devastating—particularly for universities and other non-profit institutions. As one Alzheimer's researcher noted, these lawsuits "'constitute a large drain on valuable scientific resources at a time when scientific funds are increasingly tight.'" Hayden, *supra*, at 20 (quoting

Benjamin Wolozin, Alzheimer's researcher, Boston University).

Not surprisingly, then, gene patents have made laboratories hesitant to conduct promising genetic research. A survey of more than 130 genetic laboratories revealed that fifty-three percent of respondents elected to forgo developing or performing a genetic test for clinical or research purposes because of a pre-existing patent. Mildred K. Cho et al., *Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services*, 5 J. Molecular Diagnostics 3, 5 (2003); *see also* John F. Merz, *Disease Gene Patents: Overcoming Unethical Constraints on Clinical Laboratory Medicine*, 45 Clinical Chemistry 324, 327 (1999) ("The knowledge that a patent application has been filed can influence the decision to spend the time and resources to develop a clinical test because of the uncertain risk that a patent holder will later prevent the laboratory from continuing to provide this service."); Alzheimer Research Forum, *Workshop Explores Intellectual Property Issues in Alzheimer's Disease* (Nov. 4, 2003), http://www.alzforum.org/new/detail.asp?id=901 (hypothesizing that "academic investigators may feel constrained from crossing a patented AD mouse model with other strains, even though such experiments might help uncover additional genes involved in neurodegeneration. Further, investigators and their institutions may be concerned about sharing or providing a mouse model that may be covered by a patent to their colleagues, who might use the model to identify a promising drug for AD."). Invalidating gene patents would eliminate the significant risk of costly patent litigation, thereby encouraging genetic research. The research is particularly important for Alzheimer's Disease because there is currently no known curative measure available. Alzheimer's Ass'n, *2012 Alzheimer's Disease Facts and Figures* 12 (2012), http://www.alz.org/downloads/facts_figures_2012.pdf.

B. Gene Patents Impede the Ability of Patients to Obtain a Second Opinion

Information gained from genetic tests can have a profound impact on medical decision-making. For many, the results from genetic testing can be life-altering. Kathy L. Hudson et al., *Oversight of US Genetic Testing Laboratories*, 24 Nature Biotechnology 1083, 1083 (2006).

Obtaining a second opinion is critical because even the most qualified, highly skilled medical professional can make a mistake or differ in opinions. QuantialMD, *Physician Perspectives on Preventing Diagnostic Errors* 3 (2011), *available at* http://www.quantiamd.com/q-qcp/QuantiaMD_PreventingDiagnosticErrors_Whitepaper_1.pdf. A new report from QuantialMD found that almost half of 6,400 physicians surveyed said they encounter diagnostic errors—missed, late, or wrong diagnoses—at their practice at least monthly. *Id.* About two-thirds said that up to ten percent of misdiagnoses they have experienced have directly resulted in patient harm. *Id.*

In the absence of a second opinion, laboratory errors and inaccurate test results can result in "misdiagnosis, inappropriate and/or delayed treatment, anxiety and in rare cases, even death." Hudson, *supra*, at 1089. Independent confirmatory testing is especially important, given the "implications for major medical decisions, such as whether to have a mastectomy or surgical removal of the ovaries." U.S. Dep't of Health & Human Servs., *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests: Report of the Secretary's Advisory Committee on Genetics, Health, and Society* 44 (Apr. 2010) [hereinafter SACGHS 2010 Report], *available at* http://oba.od.nih.gov/oba/sacghs/ reports/SACGHS_ patents_report_2010.pdf. A sole provider of a medical service is simply not in the best interest of the public health. *See* Decl. of Debra Leonard, M.D., Ph.D., J.A. at 271–77. Since the implications of incorrect genetic test results are grave, it is imperative that patients not be prevented from seeking a second opinion.

C. Gene Patents Limit Access to Genetic Testing for Low-Income Patients Covered by Medicaid

Patents additionally create unique issues of access for low-income Medicaid recipients who need genetic tests. These problems are not limited to Myriad's BRCA1/2 test, but also arise with other genetic tests offered by patent rights holders. SACGHS 2010 Report, *supra*, at 42–44. Gaining access to genetic testing is also particularly challenging for Medicaid patients because gene patents allow exclusive rights holders to place limits on the forms of insurance that they will accept. *Id.* at 43. Clinicians have reported access problems "when an exclusive rights holder does not accept a particular insurance, but enforces its patents to narrow or clear the market." *Id.* Specifically, two Emory University genetic counselors commented that "there are also labs [that are exclusive licensees or patent holders] that choose not to contract with Medicaid or Medicare at all." *Id.* (brackets in original). SACGHS concluded in its April 2010 report that "patient access problems . . . are caused not by any behavior by health insurers, but by an exclusive rights holder's decisions" and that "[i]f other laboratories could offer [these genetic tests], patients would have a greater chance of obtaining access [to them]." *Id.* at 44–45. A recent Kaiser Family Foundation State survey on preventive services for women under Medicaid, in which 48 states participated, noted that while all of the surveyed states cover mammograms, only "about half (30 states) cover BRCA testing and counseling services for women who are a higher risk for this genetic mutation associated with breast cancer." Kaiser Family Found., *State Coverage of Preventive Services for Women Under Medicaid: Findings from a State-Level Survey* 2 (2012), *available at* http://www.kff.org/womenshealth/upload/8330.pdf.

With this uncertain health care framework in place for Medicaid beneficiaries, the access problems created by exclusive gene patents are acute for these low-income individuals. Unfortunately, even

Medicaid recipients who live in states that cover BRCA testing have difficulty getting testing because Myriad refuses to accept their Medicaid. Lisbeth Ceriani, one of the plaintiffs, spoke candidly in the District Court about how Myriad Genetics holds Medicaid recipients' fate and future in its administrative hands because it could choose to accept or reject her Medicaid insurance:

> I am currently insured through MassHealth, a Medicaid insurance program for low-income people in Massachusetts. Although my health insurance covers genetic testing done through contracted laboratories, Myriad refuses to contract with MassHealth. I was told that Myriad refuses to accept the $1599 reimbursement rate that MassHealth offers for the test. Myriad is the only laboratory in the U.S. that provides full BRCA gene sequencing, so it is impossible for MassHealth to "contract" with another laboratory to cover this test for its insured.

J.A. at 121.

Access to genetic testing is also difficult for large segments of the Latin American/Hispanic population, who are disproportionately poor and uninsured or underinsured. Lloyd Runser, Cabrina Eagan & Danielle Olds, *The Uninsured and Underinsured*, http://www.case.edu/med/epidbio/mph p439/Safety_Nets.htm (last visited Jan. 29, 2013).[2] Recent data released by Myriad indicates that Hispanic patients who need BRCA testing need the full range and more costly BART analysis. *See* Myriad Genetic Labs., Inc., *BRCA1 and BRCA2 Prevalence Tables for Mutations Detected by Sequencing, the 5-Site Rearrangement Panel (LRP) and the BRACAnalyis Large Rearrangement Test (BART) in High Risk Patients*, http://www.myriad.com/lib/brac/BART-table-faq.pdf (last visited Jan. 24, 2013).[3] These tests are in excess of $3000 and for full range testing can exceed $4000. *See* Myriad Genetic Labs., Inc., *Advanced Beneficiary Notice of Non-Coverage, available at* http://www. myriad. com/lib/abn/Myriad-ABN.pdf. Those at risk for cancer often have no choice but to forgo potentially life-saving health care treatment because they lack either health care coverage or the resources to pay for genetic testing out-of-pocket.

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[2] *See also* Office of the Assistant Sec'y for Planning & Evaluation, U.S. Dep't of Health & Human Servs., *Overview of the Uninsured in the U.S.: An Analysis of the 2005 Current Population Survey* (2005), http://aspe.hhs.gov/health/reports/05/uninsured-cps/index.htm#race.

[3] *See also* Yale Cancer Genetic Counseling, *An Open Letter to Myriad Genetics* (July 22, 2011), http://yalecancergeneticcounseling.blogspot.com/2011/07/open-letter-to-myriad-enetics.html.

II. Human Genes and Isolated DNA Are Products of Nature and Not Patent Eligible.

The rationale for excluding human genes and genetic sequences rests upon the principles that:

> [L]aws of nature, natural phenomena, and abstract ideas are not patentable.

Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. __, 132 S. Ct. 1289, 1293 (2012) (quoting *Diamond v. Diehr*, 450 U.S. 175, 185 (1981)).

The discovery of phenomena of nature, even when previously unknown, is not patentable. *Parker v. Flook,* 437 U.S. 584, 593 n.15 (1978) ("Patentable subject matter must be new [novel]; not merely heretofore unknown." (quoting Peter D. Rosenberg, Patent Law Fundamentals § 4 at 3 (1975)); *Diamond*, 450 U.S. at 185 (excluding "laws of nature, natural phenomena, and abstract ideas"). These categorical exclusions are soundly based on the idea that "[p]henomena of nature . . . mental processes, and abstract intellectual concepts are . . . the basic tools of scientific and technological work." *Gottschalk v. Benson*, 409 U.S. 63, 68 (1972); *see Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948) ("manifestations of laws of nature [are] free to all men and reserved exclusively to none"); *Parker*, 437 U.S. at 593 n.15 (patentable inventions must not be "merely heretofore unknown," to avoid depriving the public of prior uses) (quoting Rosenberg, *supra*).

"In other words, natural phenomena, laws of nature, or abstract ideas, without more, are not considered to be 'useful arts.'" Edward C. Walterscheid, *"Within the Limits of the Constitutional Grant": Constitutional Limitations on the Patent Power*, 9 J. Intell. Prop. L. 291, 349 (2002).

These exclusions derive from the historic understanding that nature and science are the common heritage of mankind, free from appropriation by particular persons.

> If nature has made any one thing less susceptible than all others of exclusive property, it is the action of the thinking power called an idea . . . . That ideas should freely spread from one to another over the globe, for the moral and mutual instruction of man, and improvement of his condition, seems to have been peculiarly and benevolently designed by nature, when she made them, like fire, expansible over all space, without lessening their density in any point . . . .

Letter from Thomas Jefferson to Isaac McPherson (Aug. 13, 1813), in 13 The Writings of Thomas Jefferson 326, 333–34 (Albert Ellery Bergh ed., 1908).

In *Funk Bros.*, 333 U.S. at 132, the Court held that an inventor claiming a bacterial species that exhibited the property of mutual non-inhibition could not patent the bacteria, since it was merely a claim for a natural phenomena. *Id.* at 130. Nor was the combining of six types of bacteria into one product—bacteria whose individual function had only been "discovered" and not "invented"— patentable. *Id.* at 132. As the Court noted:

> There is, of course, an advantage in the combination. . . . But a product must be more than new and useful to be patented; it must also satisfy the requirements of invention or discovery. The application of this newly-discovered natural principle to the problem of packaging of inoculants may well have been an important commercial advance. But once nature's secret of the non-inhibitive quality of certain strains of the species of Rhizobium was discovered, the state of the art made the production of a mixed inoculant a simple step. Even though it may have been the product of skill, it certainly was not the product of invention. There is no way in which we could call it such unless we borrowed invention from the discovery of the natural principle itself.

Id. at 131–32 (citations omitted).

Physical steps such as isolating and removing DNA cannot transform unpatentable natural phenomena into a patentable invention. Likewise in *American Wood-Paper Co. v. Fibre Disintegrating Co.*, 90 U.S. 566 (1874), the Court found that merely removing pulp from straw, wood, or other natural sources did not make it a patentable new composition of matter: "A process to obtain it [an extract] from a subject from which it has never been taken may be the creature of invention, but the thing itself when obtained cannot be called a new manufacture." *Am. Wood-Paper*, 90 U.S. at 593–94.

In that case, American Wood-Paper sought to patent a supposedly "new" type of pulp that was better suited for the manufacture of paper than the then-existing pulp. *Id.* at 577. All pulp contains both cellulose and "intercellular matter," the latter of which must be removed to render the cellulose fit for being made into paper. *Id.* at 566. Up until this point, all pulp was removed by applying both chemical and mechanical treatment; however, American Wood-Paper managed to remove the intercellular matter using chemical means alone. *Id.* American Wood-Paper claimed that the pulp produced by mere chemical treatment alone was a "new manufacture," and thus, eligible for patent protection. *Id.* at 595.

The Court rejected the patent, holding that the new pulp was "not a new composition of matter." *Id.* at 593. The Court held as immaterial the fact that the new pulp was pure cellulose whereas the old pulp was only "approximately pure," i.e. it was still mixed with intercellular matter. *Id.* at 594.

Isolated human genes and DNA sequences are products of nature and are not patentable.

CONCLUSION

For the foregoing reasons, AARP respectfully urges the Court to grant the relief requested by petitioners and invalidate the patents.

Respectfully submitted,

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January 31, 2013

AMICUS
CURIAE
BRIEF

Supreme Court, U.S.
FILED
JAN 30 2013
OFFICE OF THE CLERK

RECORD AND BRIEFS

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

AMICI CURIAE BRIEF FOR ACADEMICS IN LAW, MEDICINE, HEALTH POLICY AND CLINICAL GENETICS IN SUPPORT OF NEITHER PARTY

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INTEREST OF THE *AMICI CURIAE*[1]

Amici Curiae are academics in law, medicine, health policy and clinical genetics. Collectively, they have advised governments in the United States, Canada, South Africa, the United Kingdom and Australia, as well as international organizations including the Organisation for Economic Co-operation and Development (OECD), the European Union and the World Health Organization on human gene patents and life science innovation. Specifically, they chaired a task force of the Secretary's Advisory Committee on Genetics, Health and Society on human gene patents, testified before Congress on genetic testing, drafted guidelines for the OECD on the licensing of genetic inventions, prepared a report for the OECD on intellectual property management in the life sciences, prepared Opinions for the European Commission on intellectual property issues in life sciences, drafted reports for the U.S. Congress, prepared multiple case studies on gene patenting in the United States and prepared submissions for Australian law reform inquiries into gene patenting.

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[1] The petitioners have filed a letter of blanket consent to filing *amicus* briefs and this letter is lodged with the Clerk. The respondents granted consent to *amici* on January 9, 2013 via electronic mail. Pursuant to this Court's Rule 37.6, the *amici* submitting this brief and their counsel hereby represent that no party to this case nor their counsel authored this brief in whole or in part, and that no person other than *amici*, using research funds provided by Value Addition through Genomics and GE3LS (VALGEN), paid for or made a monetary contribution toward the preparation and submission of this brief.

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SUMMARY OF ARGUMENT

The *BRCA1* and *BRCA2* genes, the patent-eligibility of which is contested in this case, are sequences of DNA that specify the production of protein molecules involved in detecting and repairing DNA damage. All human genes are made of molecules of deoxyribonucleic acid (DNA) that are transcribed into ribonucleic acid (RNA). DNA is the chemical storage and transmission medium of genetic information. It stores information within cells and it transmits genetic information from cell to cell, organism to organism, and generation to generation. RNA is a molecule that is essential in the translation of genetic information into proteins and possesses several regulatory functions within cells. The impugned composition-of-matter claims in this case thus constitute human genes as they claim the concrete embodiments of those genes.

This Court has recognized that 35 U.S.C. § 101 contains a single exception to patentable subject matter that comprises three components: laws of nature, abstract ideas and phenomena of nature. While *Mayo v. Prometheus*, 132 S.Ct. 1289 (2012) is this Court's latest statement on the purpose and nature of this exception, it builds on a century and a half of consistent jurisprudence. According to *Mayo*, this exception is crucial to achieving the overarching aim of patent law to facilitate rather than inhibit innovation.

Mayo builds on *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), which distinguished between claims to naturally occurring compounds and claims to inventions. According to *Chakrabarty*, to constitute an invention constituting patentable subject matter, the claimed compound must possess a 'markedly different' function than does the natural compound.

DNA inherently possesses a dual nature that has a decisive impact in determining whether the claimed inventions are 'markedly different' from their natural counterparts. First, DNA is the embodiment of information in the order of its base pairs, forming a quaternary code analogous to the binary code used in computer software. Second, it is a physical chemical with bonds, folding and other physical characteristics that determine its biochemical properties. The reduction of DNA to either a chemical or to pure information—and thus ignoring its dual nature—has led courts below, the parties and commentators to misapply the 'markedly different' test.

Because one of the natural functions of DNA and RNA is to store and transmit information, a 'markedly different' function must be something beyond these. Yet, the specification does not recite any such function in relation to many of the molecules falling within the impugned claims.

Further, the impugned claims attempt to capture the genetic information embodied within human genes. In fact, the specification specifically recites the use of the invention to retrieve this information. Information does not, however, constitute patentable subject matter under precedents of both this Court and of the Federal Circuit.

This Court held in *Diamond v. Diehr*, 450 U.S. 175 (1981) that the addition of insignificant post-solution activity does not convert a claim over unpatentable subject matter into one that was eligible for patent protection. Isolating a human gene is an example of such insignificant post-solution activity. Moreover, in the context of diagnostics, isolation is merely a byproduct of the real purpose, which is to exactly copy the information stored in a person's DNA. While the step of isolation may require technical skill, the legal test of significance of the activity is based on whether the activity itself gives a markedly different function to the invention. When the purpose of creating a DNA molecule is to reveal the genetic information it embodies—as is the case when conducting diagnostic tests or in doing science to study the *BRCA1/2* genes—isolation does not provide any additional function to a gene beyond its natural information storage function. Therefore, making an exact copy and 'isolating' the DNA is not sufficient in itself to convert the copied DNA into a patentable invention. In addition, claims over human genes that possess no function beyond their ability to store the *natural* genetic information recorded on human genes cannot be patented.

In constrast, both natural and altered DNA and RNA that possess functions beyond information storage and transmission are eligible for patent protection. To claim naturally-occurring isolated sequences, patent claims would need to be restricted to the use of the molecule for the additional function. For altered DNA and RNA molecules, the invention can normally be protected using composition-of-matter claims, provided they also satisfy §§ 102, 103, and 112 as well as § 101 utility.

ARGUMENT

The question before this Court—are human genes patentable?—asks whether and under which circumstances the molecular unit of human heredity, in the form of strands of deoxyribonucleic acid (DNA) and/or ribonucleic acid (RNA) (*see* Helen Pearson, *Genetics: What is a Gene?*, 441 NATURE 398 (2006)), constitute patentable subject matter under 35 U.S.C. § 101. DNA strands may contain the sequence of entire human genes without any deletions or editorial changes (genomic DNA or gDNA), sequences of messenger RNA that correspond (through transcription) to that gDNA, sequences of DNA that (through reverse transcription) correspond to the messenger RNA that is translated into proteins by cellular ribosomal complexes (complementary DNA or cDNA), and smaller strands of either DNA or RNA.

In the context of the present case, nine patent claims fall within the above understanding of human genes: claims 1, 2, 5, 6 and 7 of the 5,747,282 patent ('282 patent), claims 1, 6 and 7 of the 5,837,492 patent ('492 patent) and claim 1 of the 5,693,473 patent ('473 patent). These claims read, collectively, over gDNA sequences, cDNA sequences and RNA sequences, ranging in length from 15 base pairs to the entire, unedited, gene sequence for *BRCA1* and *BRCA2*.

While the context in which this case is set—health care innovation—demonstrates the social and ethical importance of the question before the Court, its answer can be determined solely on the basis of this Court's precedents on patent eligibility that stretch back well over a century. The latest of these, *Mayo v. Prometheus*, 132 S.Ct. 1289 (2012), is simply the most recent in a long and consistent line of jurisprudence.

The Effect of Broad Claims over Human Genes on Innovation

While perhaps more socially and politically charged than most patent law issues (*See, e.g.*, E. Richard Gold & Julia Carbone, *Myriad Genetics: In the Eye of the Policy Storm*, 12 (4) GENETICS MED. S39 (2010) (April supplement)), legal controversies over the patenting of human genes can be resolved through the application of this Court's precedents. Peter Yun-Hyoung Lee, *Inverting the Logic of Scientific Discovery: Applying Common Law Patentable Subject Matter Doctrine to Constrain Patents on Biotechnology Research Tools*, 19 HARV. J.L. & TECH. 79, 82 (2005).

Nowhere is the impact of broad claims over human genes more evident than in the field of human genetic testing. In a study of US and European patents affecting such testing, researchers found that, out of the 22 inherited diseases studied, 16 diseases are subject to at least one blocking patent. Isabelle Huys, *et al.*, *Legal Uncertainty in the Area of Genetic Diagnostic Testing*, 27 NATURE BIOTECHNOLOGY 903, 904 (2009).

Recent advances in DNA sequencing have led to a dramatic increase in the efficiency and scope of genetic testing. Yet the grant of patents over human genes has impeded innovation in this domain. This problem has emerged in developing a new and more comprehensive approach to test those at risk of breast and ovarian cancer. 'Deep sequencing' tests of over twenty genes are comparable in cost to the two-gene *BRCA1/2* sequence-based test offered by the Respondents. Tom Walsh et al., *Detection of Inherited Mutations for Breast and Ovarian Cancer Using Genomic Capture and Massively Parallel Sequencing*, 107 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES 12629, 12631 (2010). Commercial laboratories have begun to offer comprehensive genetic testing in a single test of almost all genes—that notably leaves out *BRCA1/2*, the human genes subject to the claims in question—that may explain inherited risk of breast or ovarian cancer.

For example, Ambry Genetics, a commercial diagnostic genetics laboratory, recently began offering sequencing of a panel of cancer genes. AMBRY GENETICS http://www.ambrygen.com/tests/breastnext (last visited December 13, 2012). The Ambry Genetics panel has the potential to be a very useful clinical test but its utility is severely undermined by the fact that the Ambry Genetics panel does not include *BRCA1/2*. These exclusions are attributable to infringement liability from the patents at issue in this case. The lack of coverage of *BRCA1/2* forces a clinician to order two expensive tests serially from two different providers when one comprehensive test would not only be less expensive, but provide more timely results to patients. As the Respondents have never licensed the sequence-based testing of *BRCA1/2* (although they have licensed testing for known individual mutations, a distinction often incompletely explained by Respondents) Respondents' patents prevent the development of a comprehensive sequence-based test of the twenty-some known genes associated with breast and ovarian cancer. While cross-licensing would theoretically enable the development of truly comprehensive tests, the industry has failed to engage in this practice for more than a decade, preferring instead to maximize revenue from single genetic tests.

In developing diagnostic tests, patent incentives play a much smaller role than in drug discovery or therapeutic biological molecules: "[P]atents have not caused irreparable harm in genetic diagnostics, but neither have they proven greatly advantageous . . . One justification for gene patents is that they speed up the development of tests. But the patent incentive is usually not necessary." Robert Cook-Deegan et al., *The Dangers of Diagnostic Monopolies,* 458 NATURE 405, 405 (2009). Out of 10 clinical conditions studied, researchers found that "in no case was the exclusive licensee [with control over the patents] the first to market." Julia Carbone et al., *DNA Patents and Diagnosis: Not a Pretty Picture,* 28 NATURE BIOTECHNOLOGY 784, 788 (2010).

This is not to say that patents have no place in the field of genetic diagnostics. In two of ten clinical conditions studied (Mercator Genetics for hemochromatosis and Myriad Genetics for breast and ovarian cancer), researchers at Duke University found that patents played a positive role in enticing private investment to supplement the public investment in genetics research. Robert Cook-Deegan et al., *Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers with Colon Cancers*, 12 GENETICS IN MEDICINE

S15 (2010); Subhashini Chandrasekharan, et al., *Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Hereditary Hemochromatosis*, 12 GENETICS IN MEDICINE S155 (2010). Despite positive outcomes being in the minority, these two cases illustrate that patents can contribute to health innovation.

The key to preserving the benefits of patents while avoiding their costs is to develop a sufficiently clear bright-line rule, as suggested by *Mayo*, 132 S.Ct. at 1303, that differentiates unpatentable human genes that inhibit innovation from 'markedly different' inventions that facilitate it. Thus, the question is *not* whether the Respondents ought to receive a patent for their work; the answer to that question is likely 'yes'. Rather, the question is whether the Respondents claimed too broadly so as not only to claim their contributions to health and science but also to exclusively control any study and use of the natural function of human genes.

A Question of Law, Not Science

This Court specifically warned against conflating legal and scientific determinations in *Diamond v. Chakrabarty*, 447 U.S. 303 (1980) and in *Mayo*. In both cases, this Court held that its role was limited to making legal determinations and not the subtle parsing of scientific knowledge and opinion.

In *Chakrabarty*, the petitioner asked the Court to resist granting a patent over a genetically-created bacterium because "[s]cientists, among them Nobel laureates. . . [suggest] that genetic research may pose a serious threat to the human race, or, at the very least, that the dangers are far too substantial to permit such research to proceed apace at this time." *Chakrabarty*, 447 U.S. at 316. This Court held that its role was to provide a legal interpretation of the patent statute, not to engage in science: "What is more important is that we are without competence to entertain these arguments—either to brush them aside as fantasies generated by fear of the unknown, or to act on them." *Chakrabarty*, 447 U.S. at 317.

Similarly, in *Mayo*, this Court held that the determination of the scope of exceptions to patentable subject matter under § 101 was a legal question, not one that depended on a deep understanding of science: "Courts and judges are not institutionally well suited to making the kinds of judgments needed to distinguish among different laws of nature. And so the cases have endorsed a bright-line prohibition against patenting laws of nature, mathematical formulas and the like, which serves as a somewhat more easily administered proxy for the underlying 'building-block' concern." *Mayo*, 132 S.Ct. at 1303.

The Federal Circuit in the decision below conflated the legal question it posed—do isolated DNA molecules constitute patentable subject matter under § 101?—with the scientific determination of how one can isolate DNA molecules. For example, the majority stated as follows:

> As the above description indicates, isolated DNA is not just purified DNA. Purification makes pure what was the same material, but was combined, or contaminated, with other materials. Although isolated DNA is removed from its native cellular and chromosomal environment, it has also been manipulated

> chemically so as to produce a molecule that is markedly different from that which exists in the body.

Association for Molecular Pathology v. USPTO, 689 F.3d 1303, 1328 (Fed. Cir. 2012) ("*AMP v USPTO*").

> In this case, the claimed isolated DNA molecules do not exist in nature within a physical mixture to be purified. They have to be chemically cleaved from their native chemical combination with other genetic materials . . . . In fact, some forms of isolated DNA may require no purification at all, because DNAs can be chemically synthesized directly as isolated molecules.

AMP v. USPTO at 1329.

These passages reveal a troubling conflation of science and law (in addition to the mistake of reducing the claimed invention to the process through which the Federal Circuit speculated it may have been produced). Rather than determine whether the claimed invention falls within the *legal* meaning of invention under § 101, the Federal Circuit answered the question of whether a scientist would use the same processes to *isolate* as to *purify* DNA molecules. The result of this approach was for the Federal Circuit, the actor entrusted with the duty to determine the legal question posed by § 101, to delegate its determination of patent eligibility to scientists and their processes.

There are two strong prudential reasons why this Court in both *Chakrabarty* and *Mayo* held that it was inappropriate to engage in a fine analysis of science when answering the legal question of whether a purported invention constitutes patentable subject matter.

First, determinations of patent-eligibility do not change over time but become established standards in the law. They do not, in particular, depend on the state of knowledge available to the person of skill in the art, whether at the moment of invention, of filing, of patent grant or of claim construction. As scientific knowledge undergoes rapid change, it is inappropriate to link a determination of patent eligibility to the particular understanding of the science at any one moment because that understanding could soon be out of date.

Second, as the decision of the majority in the Federal Circuit illustrates, deciding questions of patent eligibility on the basis of the science—or the particular technical procedural arcana of purification or isolation—leads courts to engage in speculative assessments of the state of scientific knowledge. Because subject matter eligibility is a pure question of law, the courts are not assisted by expert evidence in these determinations and thus must make their own findings about the science involved. This is precisely the confusion that the Federal Circuit introduced in the present case.

The majority opinion in the Federal Circuit misunderstood a seminal 1960s text on chemistry to hold that the defining characteristic of the DNA molecule is its set of *covalent* bonds. ("But a covalent bond is the defining boundary between one molecule and another, and the dissent's citation of Linus Pauling's comment that covalent bonds 'make it convenient for the chemist to consider [the aggregate] as an independent molecular species' underlines the point." *AMP. v. USPTO* at 1329.) The correct citation of the text reveals, however, that the defining characteristic of a molecule is a *chemical* bond, which includes "electrostatic bonds [which encompass both ionic and hydrogen bonds], covalent bonds and metallic bonds." LINUS PAULING, THE NATURE OF THE CHEMICAL BOND AND THE STRUCTURE OF MOLECULES AND CRYSTALS: AN INTRODUCTION TO MODERN STRUCTURAL CHEMISTRY 5 (3d ed. 1960). Thus, a covalent bond in the Pauling text is but one type of chemical bond that defines a molecule. The result of this misreading of the Pauling text was that the Federal Circuit majority focused exclusively on covalent bonds, when electrostatic bonds play at least as critical a role in the function of DNA as the unique storage and transmission medium of biological information.

Because of this Court's concerns over separating legal from scientific questions, it held, in *Mayo,* 132 S.Ct. at 1305, that courts ought not to engage in too fine an analysis of the science underlying the exceptions to patentability even if this results in different effects in different fields of technology. With this caution in mind, we turn to this Court's elucidation of the exception to patentable subject matter in § 101.

A Single Exception Residing in 35 U.S.C. § 101

This Court has many times recognized that there are limits to the scope of § 101. It has encapsulated these in a judicially-elaborated exception relating to laws of nature, natural phenomena and abstract ideas (e.g., *Mayo; Bilski v. Kappos*, 130 S. Ct. 3218 (2010); *Diamond v. Diehr,* 450 U.S. 175 (1981); *Chakrabarty,* 447 U.S.; *Gottschalk v. Benson*, 409 U.S. 63 (1972); *Parker v. Flook*, 437 U.S. 584

(1978); *Rubber Tip Pencil Company v. Howard*, 87 U.S. 498 (1874); *LeRoy v. Tatham*, 55 U.S. 156 (1852); *O'Reilly v. Morse* 56 U.S. (15 How.) 62 (1853)). In particular, this Court in *Mayo* provided a clear and straightforward understanding of the independent role played by this exception. This understanding has four elements.

First, *Mayo* brushed aside any uncertainties introduced by the Federal Circuit (*MySpace Inc., v. GraphOn Corp.*, 672 F.3d 1250 (2012)) over whether a § 101 determination of patentable subject matter must take place prior to any §§ 102, 103, and 112 or § 101 utility analyses. ("These considerations lead us to decline the Government's invitation to substitute §§ 102, 103, and 112 inquiries for the better established inquiry under § 101." *Mayo*, 132 S.Ct. at 1304.) "[T]o shift the patent-eligibility inquiry entirely to these later sections risks creating significantly greater legal uncertainty, while assuming that those sections can do work that they are not equipped to do." *Mayo*, 132 S.Ct. at 1304. That is, *Mayo* made clear that determination of patent-eligibility is the first step in the analysis of the validity of any patent claim. While for most claims this step is so evident that it can effectively be skipped, courts must logically determine whether the claim reads over a patent-eligible invention before determining whether that invention complies with the substantive criteria of novelty, utility and obviousness, as well as those relating to description and enablement.

Second, § 101 implicitly contains *one* overarching exception with three components—laws of nature, natural phenomena and abstract ideas—and not three distinct exceptions. ("The Court has long held that this provision contains *an* important implicit exception.

'[L]aws of nature, natural phenomena, and abstract ideas' are not patentable." *Mayo,* 132 S.Ct. at 1293, citations omitted, emphasis added.) The three components are simply different ways to address aspects of one central, principled exception rather than constituting three, narrow, watertight and independent exceptions. This is illustrated in *Mayo* by the Court's reliance on cases falling into each of the three components (*O'Reilly v. Morse,* (15 How.) 62 (1854) with respect to laws of nature; *Funk Brothers Seed Col v. Kalo Inoculant Col,* 333 U.S. 127 (1948) and *Chakrabarty* regarding natural phenomena; *Diamond v. Diehr,* 450 U.S. 175 (1981), *Parker v. Flook,* 437 U.S. 584 (1978), and *Bilski v. Kappos,* 130 S.Ct. 3218 (2010) dealing with abstract ideas) to elucidate the central purpose underlying the exception. In fact, the *Mayo* Court held that two cases, *Diehr* and *Flook,* both of which relate to *abstract ideas,* were "most directly on point" in relation to the *law of nature* at issue in *Mayo. Mayo,* 132 S.Ct. at 1298.

Third, the underlying purpose behind the exception is to avoid the "danger that the grant of patents that tie up [the] use [of laws and principles] will inhibit future innovation premised upon them, a danger that becomes acute when a patented process amounts to no more than an instruction to 'apply the natural law,' or otherwise forecloses more future invention than the underlying discovery could reasonably justify." *Mayo,* 132 S.Ct. at 1301, citations omitted. The Court recognized that patent law must consider both the facilitative and inhibitory effects of patents so as to maximize innovation:

> Patent protection is, after all, a two-edged sword. On the one hand, the promise of exclusive

> rights provides monetary incentives that lead to creation, invention, and discovery. On the other hand, that very exclusivity can impede the flow of information that might permit, indeed spur, invention, by, for example, raising the price of using the patented ideas once created, requiring potential users to conduct costly and time-consuming searches of existing patents and pending patent applications, and requiring the negotiation of complex licensing arrangements.

Mayo, 132 S.Ct. at 1305.

Fourth, the exception flows from the policy inherent in the patent laws as passed by Congress, not from definitions and concepts deriving from particular branches of science. ("[P]atent law's general rules must govern inventive activity in many different fields of human endeavor, with the result that the practical effects of rules that reflect a general effort to balance these considerations may differ from one field to another." *Mayo,* 132 S.Ct. at 1305). That is, the determination of patent eligibility is, as argued earlier, a pure question of law and not one that ought be delegated to scientists or technicians.

As the question of the patent-eligibility of human genes has never been directly raised, the application of this unitary principle (with three components) to the claims in issue provides a straightforward means of answering that question.

'Markedly Different' Refers to Functional Difference

Mayo made clear that there is a single, underlying, purpose behind the judicially recognized exception to patent-eligibility under § 101: that claims may not encompass so much intellectual territory that they diminish, as opposed to facilitate, the flow of information that is essential to further innovation. While stated using contemporary language, this purpose has long been embedded in this Court's decisions concerning all three facets of the exception.

This Court's elucidation of the exception in *Chakrabarty* embodies this purpose. There, this Court held that, to constitute patentable subject matter, the claimed invention must possess "markedly different characteristics from any found in nature". *Chakrabarty*, 447 U.S. at 310. In contrast to the claimed invention in *Funk Brothers*, which the *Chakrabarty* Court stated had no "different use" than what was found in nature, Chakrabarty's invention carried out a new and useful function. *Chakrabarty*, 447 U.S. at 310. ("This human-made... bacterium is capable of breaking down multiple components of crude oil. Because of this property, which is possessed by no naturally occurring bacteria, [the] invention is believed to have significant value. . . ." *Chakrabarty*, 447 U.S. at 305).

By focusing on the functional difference between the claimed invention and its natural counterpart, the *Chakrabarty* Court was able to distinguish between inventions that contributed to future innovation (those that have a markedly different function) and those that hindered innovation (those that tied up an important natural phenomenon that lay at the heart of a great swath of potential innovation).

It is through an understanding of this underlying purpose—as highlighted in *Mayo*—that it becomes clear that the *Chakrabarty* test is related to functional instead of simply structural differences between claimed inventions and their natural counterparts. While a structural difference will usually result in a functional difference, it is the functional and not the structural difference that meets the legal test of patent eligibility.

Applying *Chakrabarty* in light of *Mayo*, the question before the Court reduces to whether claims reading over human genes or parts of them are functionally different from those same genes occurring in their natural form. Where the function of the claimed invention is 'markedly different' from that of the natural counterpart, it is patent-eligible; where the claimed invention carries out the same function as the natural counterpart, it is not.

DNA's Dual Nature

DNA inherently has a dual nature. It is both a molecule and medium for storing genetic information for operations within a cell and transmitting that information from cell to cell, organism to organism, and generation to generation: "DNA sequences are not simply molecules; they are also information. Knowing the DNA sequence for the genome of an organism provides valuable scientific information that can open the door to future discoveries." Rebecca S. Eisenberg, *How Can You Patent Genes?*, 2 AM. J. BIOETHICS, 30 Nov. 2010, at 3, 4 (2002). Because of this duality, the granting of patents over DNA has been controversial with scientists, physicians and policy-makers: "[T]he central problem with human DNA sequence patents today is that they not only provide their holders with control over the invention itself—the physical molecule—but also over access to the particular health information coded in individual genes." E. Richard Gold, *Gene Patents and Medical Access,* 49 INTELL. PROP. F. 20, 24 (2002).

Information is the building block of ideas and concepts. As such, information is understood not to constitute patentable subject matter:

> Patent rights are not well adapted to protecting information, particularly information about the natural world. Given that independent discovery of such information is quite likely to happen without the efforts of any particular patent holder, excessive protection of such information as intellectual property may slow down subsequent research more than it promotes the original data collection.

Rebecca S. Eisenberg, *Patenting Genome Research Tools and the Law,* 326 COMPTES RENDUS BIOLOGIES 1115, 1118 (2003); *see also In re Comiskey*, 554 F.3d 967, 978-980 (Fed. Cir. 2009).

An applicant cannot simply impose a new function on information by restricting the claim to a particular technological environment. *See, e.g., Diamond v. Diehr,* 450 U.S. at 191 ("A mathematical formula as such is not accorded the protection of our patent laws, and this principle cannot be circumvented by attempting to limit the use of the formula to a particular technological environment.") (citations omitted).

Similarly, an applicant cannot turn an unpatentable claim to information into a patentable claim simply by limiting the invention to a particular medium without also indicating the additional function that embodying this information on that medium accomplishes. *See In re Bradley*, 600 F.2d 807, 812 (C.C.P.A. 1979). This conclusion is illustrated through a consideration of the 'printed matter' doctrine in *King Pharmaceuticals, Inc. v. Eon Labs, Inc.*, 616 F.3d 1267 (Fed. Cir. 2010).

"Roughly stated, [the 'printed matter' doctrine] dictates that 'information recorded in [a] substrate or medium' is not eligible for patent protection—regardless of how nonobvious and useful it is—if the advance over the prior art resides in the 'content of the information.'" Kevin E. Collins, *Semiotics 101: Taking the Printed Matter Doctrine Seriously*, 85 IND. L.J. 1379, 1380 (2010) ("*Semiotics 101*").

King Pharmaceuticals involved a claim to dispensing a known medicine while informing patients to take the medicine with food and another claim to dispensing that medicine in conjunction with a printed label that informed the patient to take the medicine with food. The Federal Circuit rejected both claims, noting that:

> In an analogous context, we have held that '[w]here the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability.' . . . In such cases, we have recognized that the printed matter is not independently patentable . . .

King Pharmaceuticals, 616 F.3d at 1278-79 (citations omitted).

The Federal Circuit held that there was no functional relationship between the information provided—to take the medicine with food—and the medicine itself. *Id.* at 1279.

While the information of taking medicine with food does not constitute patentable subject matter in itself, that information could result in a patentable invention if limited to an embodiment in a specific medium or to a context in which doing so has a functional advantage. This was the case in *In re Gulack*, 703 F.2d 1381 (Fed Cir. 1983), in which the Federal Circuit held as patentable an invention consisting of a series of numbers that, when printed on a circular band, served the function of educating about number theory. While the information itself was too abstract to be patented, that information when recorded on the particular medium served a specific function that neither the numbers themselves nor their being printed on another medium—for example, a sheet of paper—accomplished. *See Id.* at 1386-87.

Despite the fact that the *King Pharmaceuticals* Court applied the 'printed matter' doctrine under 35 U.S.C. § 103, the same analysis can be applied often more persuasively under 35 U.S.C. § 101. *See, e.g., In re Nuijten*, 500 F.3d 1346, 1365 (Fed. Cir. 2007) (Linn, J., concurring-in-part and dissenting-in-part); *Semiotics 101* at 1380 n. 1 ("The Federal Circuit grounds the printed matter doctrine alternately in 35 U.S.C. §§ 101 & 103, but there is no principled basis for the statutory distinction").

One of the critical rulings in *King Pharmaceuticals* was the court's extension of the printed matter' doctrine to a large range of media:

> Although these 'printed matter' cases involved the addition of printed matter, such as written instructions, to a known product, we see no principled reason for limiting their reasoning to that specific factual context.

King Pharmaceuticals, 616 F.3d at 1279.

While information cannot be claimed *as* information, even when embodied in a medium, it is nonetheless clear that when the restriction of the information to a particular medium serves some function beyond imposing a physical limit on the claim, then the claim recites patentable subject matter:

> More than mere abstraction, the data structures are specific electrical or magnetic structural elements in a memory. According to Lowry, the data structures provide tangible benefits: data stored in accordance with the claimed data structures are more easily accessed, stored, and erased. . . . In short, Lowry's data structures are physical entities that provide increased efficiency in computer operation.

In re Lowry, 32 F.3d 1579, 1583-1584 (Fed. Cir. 1994).

When the invention involves information that is necessarily tied to the medium on which information is stored, as were the data structures in *In re Lowry*, then the invention constitutes patentable subject matter under § 101. On the other hand, where the embodiment of information on a particular medium implies no particular function beyond holding the information it contains, then that limitation cannot save the claim from invalidity under § 101.

The case law thus treats the two aspects of human genes differently. To the extent that a claim reads over DNA or RNA that carries out the information storage and transmission function of a human gene, it does not constitute patentable subject matter. On the other hand, claims relating to DNA and RNA would satisfy the patentable subject matter test when the patent is directed to a biochemical function attached to the form of molecule claimed (*e.g.*, gDNA, RNA or cDNA) that goes beyond simple storage and transmission of the information encoded in the gene. For example, DNA (even if identical to a natural sequence) within a construct for gene therapy, inserted into a bacterium or other organism to produce a given protein, modified to have new characteristics, forming a replicon, tagged as a probe, or DNA injected into the body to encode proteins that elicit a vaccine response, would all have this additional function.

Isolation Constitutes Insignificant Post-solution Activity

Diehr further developed this Court's elaboration on the underlying purpose of the § 101 exception, particularly in relation to its discussion of *Parker v. Flook*, 437 U.S. 584 (1978). In *Flook*, the patent applicant claimed "a formula for computing an updated alarm limit," *Flook*, 437 U.S. at 586, to help an operator identify when to terminate a chemical reaction. The *Diehr* Court explained that, while the applicant had argued that the calculation of the alarm limit was a critical component of the underlying chemical reaction, in reality, the alarm limit constituted nothing more than insignificant post-solution activity. *Diehr*, 450 U.S. at 191.

The Court's discussion of function and post-solution activity further reveals the workings of the § 101 exception:

> Similarly, insignificant post-solution activity will not transform an unpatentable principle into a patentable process. To hold otherwise would allow a competent draftsman to evade the recognized limitations on the type of subject matter eligible for patent protection. On the other hand, when a claim containing a mathematical formula implements or applies that formula in a structure or process which, when considered as a whole, *is performing a function which the patent laws were designed to protect* (*e. g.*, transforming or reducing an article to a different state or thing), then the claim satisfies the requirements of § 101.

Diehr, 450 U.S. at 191-192 (citations omitted; emphasis added).

It is thus not just any human intervention that converts a natural law, an abstract idea or (as in the present case) a phenomenon of nature into patentable subject matter: that human intervention must also result in a markedly different function. As *Chakrabarty* made clear, that function must be other than the function of the phenomenon of nature; that is, in this case, it must be something other than the storage and transmission of genetic information.

The Federal Circuit placed much emphasis on the fact that the impugned claims were restricted to 'isolated' molecules:

> Accordingly, *BRCA1* and *BRCA2* in their isolated states are different molecules from DNA that exists in the body; isolated DNA results from human intervention to cleave or synthesize a discrete portion of a native chromosomal DNA, imparting on that isolated DNA a distinctive chemical identity as compared to native DNA.

AMP v. USPTO at 1328.

The majority in the Federal Circuit arrived at this conclusion not on the basis of applying the legal test of patentable subject matter as elucidated by this Court in *Mayo, Chakrabarty* and *Flook* but on the basis of its own, disputable, scientific inquiry into the process of isolating and synthesizing human genes. In ignoring the required inquiry into whether the step of isolation gives rise to a 'markedly different' function (*Chakrabarty,* 447 U.S. at 310) or a "function which the patent laws are designed to protect" (*Diehr,* 450 U.S. at 192), the Federal Circuit effectively substituted a 'chemical structural difference test' for the legal one. In doing so, it not only introduced a legal error but as noted earlier, in misunderstanding the scientific texts from which it quoted, scientific error as well.

To determine whether isolation of a human gene *by itself* introduces a markedly different function as required by *Chakrabarty* and *Diehr*, one must return to the natural function of those genes: to store and transmit information. Since isolation does nothing to alter or improve this function, the answer, following this Court's precedents, is clear: no.

The answer would be different if, in addition to isolation, a new function were introduced. DNA molecules used to treat a disease by gene transfer or to make a therapeutic protein would not be merely isolated but have an additional, patent-eligible, function. Here, however, the 'isolated' molecule, like the original, has no function beyond the storage and transmission of information.

In fact, the only function suggested in the specification of the '282 patent for an isolated, unaltered and unedited molecule of gDNA (as included within Claim 1 of that patent) is to extract the *information* stored on it. '282 Patent, col. 12, ll. 42-44 ("The finding of *BRCA1* mutations thus provides both diagnostic and prognostic *information*") (emphasis added); *Id.* at col. 28, ll. 26-28 ("Results of these tests and interpretive *information* are returned to the health care provider for communication to the tested individual") (emphasis added).

Beyond the fact that the specification does not suggest any function above the natural one of storing and transmitting information, any attempt to 'improve' the molecule by altering its sequence would make it useless for diagnostic purposes because it would no longer accurately convey the genetic information contained within the tested person's cells. Indeed, the only value to the isolated molecule is that the sequence of base pairs exactly corresponds to that of the human gene in a specific person's cells. Modifying the molecule in any way destroys this correspondence and renders the molecule useless for diagnostic purposes. A purported 'invention' that cannot, even theoretically, improve on the underlying natural phenomenon can hardly be considered an invention.

While claiming an 'isolated' gDNA molecule implies there has been some type of human intervention, that intervention does not give rise to a 'markedly different' function as required by *Chakrabarty*. Rather, the intervention constitutes the type of insignificant post-solution activity so criticized in *Diehr*. The claim is, in substance, a claim to the information contained in the human gene masquerading as a composition-of-matter claim. Since a claim to information cannot be saved by limiting it to a particular storage medium, the addition of the requirement of isolation adds "insignificant post-solution activity" to an otherwise unpatentable claim. *Diehr*, 450 U.S. at 191.

Respondents assert, in both their brief to this Court prior to the grant of *certiorari*, and before the Federal Circuit, that claims over 'isolated' DNA molecules are sufficiently narrow in scope as to not prevent the use of currently available technologies to identify mutations such as whole genome sequencing. Yet, beyond the fact that its patents have prevented the development of new diagnostic tests such as the Ambry Genetics panel, this assertion has never been evaluated: "Because no court in the United States has ever addressed this issue head-on, it is impossible to entirely rule out the possibility that a court would interpret a claim to an isolated DNA molecule in the extremely broad sense . . . " Christopher M. Holman, *Debunking the Myth that Whole-Genome Sequencing Infringes Thousands of Gene Patents*, 30 NATURE BIOTECHNOLOGY 240, 242 (2012). While Respondents have argued in these proceedings that the claims in issue do not prevent a number of general diagnostic approaches, they have not committed themselves to this position. Under the Federal Circuit's jurisprudence on issue estoppel, the Respondents will be free to argue that a particular diagnostic test falling within one of those general diagnostic approaches infringes on its claims. *SanDisk Corp. v. Memorex Products Inc.*, 415 F.3d 1278 at 1291 (Fed. Cir. 2005). Until a court has interpreted the Respondents' claims, one cannot be certain of their scope.

In addition, the Respondents' argument is not relevant. Simply because a post-solution activity, here isolation, restricts some, but not all, uses of human genes does not render it any more eligible for patent protection. As this Court warned in *Diehr*, the principle prohibiting patents on laws of nature, abstract ideas and phenomena of nature "cannot be circumvented by attempting to limit the use . . . to a particular technological environment." *Diehr*, 450 U.S. at 191. The question is not, therefore, which activities the Respondents say do not fall within the scope of their claims, but whether the Respondents have invented something that has a 'markedly-different' function from that which occurs in nature.

Where the patent applicant identifies a function in addition to that of information storage and transfer for an isolated but otherwise unaltered and unedited DNA or RNA molecule, the applicant is—provided the invention also satisfies §§ 102, 103, and 112 and the utility requirement in § 101—entitled to a claim over the use of that molecule for that new function. Claims in this form provide the inventor with appropriate recognition for his or her contribution without encumbering future innovators with claims reading over the natural function of those molecules. That this is a rational and balanced solution is illustrated by the fact that both Germany and France, two important competitors in the world of health innovation, have arrived at this same position. Section 1a(4) of Germany's *Patentgesetz* (Patent Law), 1981 BGBI as amended, requires that claims reading over molecules identical to a whole or part of a human gene must be restricted to the specific utility (industrial application) identified by the inventor. Similarly, Article L611-18 of France's *Code de propriété intellectuelle* (Intellectual Property Code) limits a claim reading over a component of the human body, including the entire or partial sequence of a human gene, to the utility specified by the inventor.

Claims at Issue

Claim 1 of the '282 patent is illustrative of the composition of matter claims in this case. It claims: "An isolated DNA coding for a *BRCA1* polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2." SEQ ID NO:2 is the naturally occurring sequence of the protein encoded by the *BRCA1* gene. To interpret this claim, recourse must be made to the specification, which defines the term DNA and describes the functions attached to DNA. *In re Suitco Surface, Inc.*, 603 F.3d 1255, 1260 (Fed. Cir. 2010) ("Rather, claims should always be read in light of the specification and teachings in the underlying patent").

The specification demonstrates that the use of the term 'DNA' as used in Claim 1 refers to unaltered genomic DNA, cDNA and altered forms of both. '282 Patent, col. 19, ll. 51-56. ("The polynucleotide compositions of this invention include RNA, cDNA, genomic DNA, synthetic forms, and mixed polymers, both sense and antisense strands, and may be chemically or biochemically modified or may contain non-natural or derivatized nucleotide bases, as will be readily appreciated by those skilled in the art.") Claim 1 restricts the set of DNA to those that have been 'isolated'. 'Isolate' and its cognates are used in many different senses in the patent specification but the explicit definition provided is as follows: "An 'isolated' or 'substantially pure' nucleic acid (e.g., an RNA, DNA or a mixed polymer) is one which is substantially separated from other cellular components which naturally accompany a native human sequence or protein, e.g., ribosomes, polymerases, many other human genome sequences and proteins." '282 Patent, col. 19, ll. 8-13. Thus, the inventors made clear that Claim 1 of the '282 patent includes, among other forms of DNA, isolated but otherwise unaltered gDNA. As noted earlier, the specifications provide no function for this gDNA other than its natural function of storing and transmitting information.

On the other hand, the specification does attribute functions beyond information storage to other molecules (i.e., other than the full gDNA molecule) falling within the broad scope of Claim 1 of the '282 patent. For example, the specification states that isolated cDNA coding for the SEQ ID NO.2 may be used in gene therapy (the genomic DNA being well known at the time to be too large for insertion within a vector. *See generally,* JOSEPH SAMBROOK & DAVID W. RUSSELL, LABORATORY CLONING; A LABORATORY

MANUAL (3d ed. 2001)). One function attributed to small portions of isolated DNA is their use as probes or primers for diagnostic or other purposes. These are non-trivial functions and their protection, through the grant of a patent, would facilitate rather than lessen innovation. Thus, if considered alone, these molecules could have been claimed for their use in relation to their additional function (beyond information storage and transmission).

The respondents did not, however, separate out their claims, preferring the broader scope of Claim 1 of the '282 patent as drafted. If they had adopted a more conservative patent strategy, they could have saved a substantial and important component of Claim 1 of the '282 patent and other impugned claims. In particular, the respondents could have adopted a less broad definition of DNA that excluded, in this case, unaltered gDNA, which specifies the protein defined by SEQ ID NO:2 and could have formulated their claims as a method of use of DNA for any of the non-natural functions. Potentially valuable subsequences of gDNA, particularly those found in the non-coding intron regions, could have given rise to valid claims under a number of circumstances. As an example, if a piece of DNA is found to bind competitively to an enhancer or promoter region in one of these introns, it could have the workings of a therapeutic molecule rather than of a storage medium for information and would be patentable for this function. Additionally, therapeutic molecules that target the intron sequences (e.g., to promote or inhibit gene expression) would constitute patentable subject matter as they have additional biochemical function. The respondents could (and did, in unchallenged claims) claim probe molecules that bind to specific sequences of interest, or primers to direct DNA synthesis.

Other claims of the impugned composition of matter claims, such as Claims 5 and 6 of the '282 patent, appear on their surface to be less broad, but in reality cover virtually any human gene. In particular, these claims include any molecule containing at least any given 15 base pair sequence occurring within any DNA sequence that would produce the *BRCA1* protein in SEQ ID 2. Claim 5 specifies over 1.6 million 15 base pair sequences, and an indefinite (thus infinite) number of DNA molecules that contain those sequences. Thomas B. Kepler, Colin Crossman and Robert Cook-Deegan, *Metastasizing Patent Claims on BRCA1*, 95 GENOMICS 312, 312 (2010). Searches of DNA sequences available before the patent was issued show that chromosome 1 alone had 340,000 sequences that fit this description, and the average gene would include 14 sequences conforming to the claim—including several genes already in the public domain before the patent application was filed. *Ibid* at 313. Subsequent analysis by the same authors indicates that long DNA sequences of well over 100 base pairs—which would be unique if DNA sequences were truly random—are found repeatedly in the human genome. Remarks to the United States Patent Office, Observations from Studies of Patenting and Licensing Practices that Affect DNA-Based Clinical Testing, app. b. (Jan. 10, 2013), http://www.genome.duke.edu/centers/cpg/sec-27study/documents/Cook-DeeganCpGstmtforUSPTOroundtable10Jan2013presentationdraft-1.docx; permission to cite obtained. The effect of the outcome of these studies is that anybody conducting a diagnostic test—whether in the course of discovery science or the study of another disease—on virtually any human gene would almost certainly produce isolated DNA molecules meeting the description of Claims 5 and 6, and thus infringe the '282 patent.

A reading of some of the non-impugned claims in the '282 patent reveal that they, in contrast with the claims examined above, constitute patentable subject matter. These would include Claims 8 to 13, all of which involve the use of the polynucleotide as a biochemical agent in addition to or instead of as an information storage and transmission medium. Whether these claims will survive a utility, novelty, non-obviousness, written description or enablement analysis is a separate question that does not arise in this case.

CONCLUSION

Following this Court's jurisprudence, human genes are patentable when claims are directed to a function that is markedly different from the genes' natural functions of genetic information storage and transmission. Hence, where the claim reads over a molecule corresponding to a naturally occurring human gene sequence, the claim must be restricted to the use of that molecule for that additional function. Where the claim reads over molecules corresponding to an altered version of the human gene sequence, unless the alteration is insignificant (e.g., if one base pair is substituted for another without changing the coding for, in the appropriate coding frame, the amino acid), then that molecule may be eligible as a composition-of-matter claim.

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AMICUS
CURIAE
BRIEF

Supreme Court, U.S.
FILED
MAR 14 2013
OFFICE OF THE CLERK

No. 12-398

In the Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL,
PETITIONERS

v.

MYRIAD GENETICS, INC., ET AL.

*ON WRIT OF CERTIORARI
TO THE UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT*

BRIEF OF THE AMERICAN BAR ASSOCIATION *AS AMICUS CURIAE* IN SUPPORT OF RESPONDENTS

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QUESTION PRESENTED

Are human genes patentable?

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INTEREST OF THE *AMICUS CURIAE*[1]

The American Bar Association ("ABA") respectfully submits this brief in support of respondents Myriad Genetics, Inc. and the University of Utah Research Foundation. The ABA urges the Court to hold that isolated DNA compounds, corresponding to genes from humans or any other organisms that do not occur in nature in their isolated form ("Isolated DNA Compounds"), are not *per se* disqualified from patent-eligibility under 35 U.S.C. § 101. Further, the ABA also urges that determinations as to the patentability of Isolated DNA Compounds should continue to be made on a claim-by-claim basis consistent with the common-law tradition of incremental determination of patent-eligibility, and that the determination of patent-eligibility is distinct from, and should be made independently of, any considerations of the other requirements for obtaining a patent.

The ABA is the largest voluntary professional membership organization and the leading organization of legal professionals in the United States. Its nearly 400,000 members come from all fifty states and other jurisdictions, and include attorneys in private law firms, corporations, non-profit organizations, government agencies, and prosecutor and public defender offices. They also include judges, legislators, law professors, law students, and nonlawyer "associates" in related fields.[2]

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[1] No counsel for a party authored this brief in whole or part, and no counsel or party made a monetary contribution to fund the preparation or submission of this brief. No person other than the *amicus curiae*, their members, and their counsel made any monetary contribution to its preparation and submission. The parties have consented to this filing.

The ABA's Section of Intellectual Property Law ("IPL Section") is the world's largest organization of intellectual property professionals. Its approximately 25,000 members represent patent owners, accused infringers, individual inventors, large and small corporations, research institutions, and public and private colleges and universities across a wide range of technologies and industries. Formed in 1894, the IPL Section works to promote the development and improvement of intellectual property law and takes an active role in the consideration of proposed legislation, administrative rule changes and international efforts. The Section also presents resolutions to the ABA House of Delegates for adoption as ABA policy. These policies then provide a basis for the preparation of ABA *amicus curiae* briefs, which are filed primarily in this Court and the Court of Appeals for the Federal Circuit.[3]

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[2] Neither this brief nor the decision to file it should be interpreted to reflect the view of any judicial member of the ABA. No member of the Judicial Division Council participated in the adoption or endorsement of the positions in this brief, nor was it circulated to any member of the Judicial Division Council before filing.

[3] Only recommendations adopted by vote of the ABA's House of Delegates, but not the accompanying reports, become ABA policy. The House of Delegates is composed of 560 delegates representing states and territories, state and local bar associations, affiliated organizations, sections and divisions, ABA members and the Attorney General of the United States, among others. See ABA General Information, *available at* http://www.americanbar.org/groups/leadership/delegates.html, and ABA amicus brief information, *available at* http://www.americanbar.org/amicus.

Through a process for articulating and adopting a consensus position of the diverse members of the legal profession working in this field, the IPL Section developed proposed recommendations regarding the proper disposition of this case. These resolutions were adopted by the ABA's House of Delegates and, with their accompanying reports, are set out in full in the Appendices as ABA Resolution 111 (policy adopted Feb. 4, 2011) and ABA Resolution 101A (policy adopted February 11, 2013).

These ABA policies support a methodology that allows for a measured, balanced approach to the determination of patent-eligible subject matter. They support a patent-eligibility assessment of Isolated DNA Compounds that is no different than the assessment of other materials that are derived from or otherwise relate to natural materials or sources. The same rationale argues against the *per se* disqualification of Isolated DNA Compounds from patent eligibility under 35 U.S.C. § 101 or the adoption of any "product of nature" doctrine that would automatically require the exclusion of such compounds from patent eligibility.

The extensive collaborative process undertaken in formulating this policy reflects a consensus conclusion of legal professionals working in this field that the determination of patent-eligibility should continue to be developed incrementally, rather than through categorical exclusions that would unreasonably stifle innovation by undermining longstanding biotechnology industry expectations and needs.

SUMMARY OF ARGUMENT

The ABA submits that this Court should hold that Isolated DNA Compounds, corresponding to genes from humans or any other organisms that do not occur in nature in their isolated form, are eligible for patenting under 35 U.S.C. § 101. To hold otherwise would be a material change in this Court's approach to determining the patent-eligibility of new technologies and upset decades of reliance on this Court's precedent, the Patent and Trademark Office's longstanding practice to allow claims to such subject matter, and Congress's evident approval of that practice.

This Court's recent decision in *Mayo Collaborative Servs.* v. *Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012) ("*Mayo*") does not change the analysis of the question presented here. *Mayo* dealt with distinguishing between method claims directed to a law of nature or the application of a law of nature. Here, the sole question before the Court is whether Myriad's compositions are a human-made invention or a product of nature. Under this Court's applicable precedent, because Myriad's Isolated DNA Compounds are not found in nature, they are eligible for patenting.

Finally, the ABA also urges that the Court set aside considerations relating to whether the subject matter claimed by Myriad is novel, nonobvious or sufficiently described and enabled in determining the patent-eligibility of Myriad's claims. Subject matter eligibility is a separate and distinct inquiry from, and resolved independently of, the other statutory requirements and conditions for patentability.

ARGUMENT

I. Categorical Disqualification of Isolated DNA Compounds, Human or Otherwise, from Patent-Eligibility Would Be a Material Change in this Court's Approach to Determining Patent Eligibility and Would Undercut Reasonable Investment-Backed Expectations and Needs.

Isolated DNA Compounds, corresponding to genes from humans or any other organisms that do not occur in nature in their isolated form, should remain patent-eligible subject matter. A *per se* or categorical disqualification of such claims would be a material change in this Court's traditional approach to determining patent-eligibility and would unjustifiably undercut significant investment-backed expectations and needs of the biotechnology industry, which has reasonably relied on longstanding precedents of this Court and others. The ABA therefore endorses the Court's continued application of its traditional incremental, common-law approach to determining the patent-eligibility of claimed subject matter.

Section 101 makes eligible for patent "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." 35 U.S.C. § 101. This Court has repeatedly recognized the "extremely broad" scope of eligible subject matter under § 101. *J.E.M. Ag Supply, Inc.* v. *Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 130 (2001) (citing *Diamond* v. *Chakrabarty*, 447 U.S. 303, 308 (1980)). "In choosing such expansive terms * * * modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope." *Bilski* v. *Kappos*, 130 S. Ct. 3218, 3225 (2010) (quoting *Chakrabarty*, 447 U.S. at 308). Because "[t]he subject-matter provisions of the patent law have been cast in broad terms," Congress need not "expressly authorize protection for new patentable subject matter," *J.E.M. Ag Supply*, 534 U.S. at 130-131 (citing *Chakrabarty*, 447 U.S. at 315), and the Court has recognized only "three specific exceptions" to the otherwise expansive language of § 101: "laws of nature, physical phenomena, and abstract ideas." *Bilski*, 130 S. Ct. at 3225 (quoting *Chakrabarty*, 447 U.S. at 309).

This Court has uniformly applied these principles incrementally to determine the patent eligibility of compositions and other subject matter; it has scrupulously avoided adopting "categorical rule[s] denying patent protection" in new, unforeseen, areas that "would frustrate the purposes of the patent law." *Bilski*, 130 S. Ct. at 3227 (quoting *Chakrabarty*, 447 U.S. at 315). For example, upon the advent of genetic engineering, the Court rejected efforts to categorically exclude living things from patent-eligibility and instead determined that claims directed to a genetically engineered bacterium were patent-eligible as directed to a "nonnaturally occurring manufacture or composition of matter." *Chakrabarty*, 447 U.S. at 309; see also *J.E.M. Ag Supply*, 534 U.S. at 133 (declining to exclude plants from patent-eligibility). More recently, in *Bilski*, the Court declined to adopt a categorical exclusion of "business methods" from § 101 "that might have wide-ranging and unforeseen impacts" on yet-to-be developed technology. *Bilksi*, 130 S. Ct. at 3227-3230. Instead, the Court resolved the case "narrowly" in view of its precedent prohibiting the patenting of abstract ideas. *Id.* at 3229. Likewise, the standards used to determine the patent-eligibility of the Isolated DNA Compounds at issue here should be the same as those used to determine the patent-eligibility of other compositions derived from or related to natural materials. See *Chakrabarty*, 447 U.S. at 309-310. There is no basis in the language of § 101, or in the case law construing that provision, for treating Isolated DNA Compounds differently. Indeed, a departure from this Court's previously uniform approach to determining patent-eligibility would frustrate practitioners' ability to reliably advise clients on the patent-eligibility of new technologies. The ABA thus endorses this Court's continued reluctance to categorically exclude subject matter from patent-eligibility in favor of the determination of patent-eligibility under § 101 in an incremental manner.

The Court's traditional incremental approach to addressing patent-eligibility has the further benefit of retaining for Congress its role in determining the boundaries of patent law as new, unforeseen technologies emerge. "Congress employed broad general language in drafting § 101 precisely because such inventions are often unforeseeable." *Chakrabarty*, 447 U.S. at 316. Against that backdrop, this Court has recognized that the categorical exclusion of unforeseen, but otherwise patent-eligible, subject matter from § 101, is "a matter of high policy" best left to "the political branches of the Government." *Id.* at 317, see also *Bilski*, 130 S. Ct. at 3228, *J.E.M. Ag Supply*, 534 U.S. at 145-146; *Mayo,* 132 S. Ct. at 1305.

To date, those branches of the government have not excluded Isolated DNA Compounds from patent-eligibility. Indeed, a categorical rule excluding Isolated DNA Compounds from patent-eligibility would reverse well over a decade of policy of the Patent and Trademark Office ("PTO") expressly allowing such claims. The PTO first issued claims relating to human genes in the early 1980s. Eric J. Rogers, *Can You Patent Genes? Yes and No*, 93 J. Pat. & Trademark Off. Soc'y 19 (2011). In 2001, relying in part on this Court's longstanding precedent, the PTO issued guidance reaffirming that claims directed to such compounds are eligible for patenting. See Utility Examination Guidelines, 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001) (stating that isolated genes are eligible subject matter as compositions of matter not found in nature).

In the 30 years since the PTO began issuing claims directed to human genes, Congress has not expressed any disagreement with the PTO's policy of allowing claims to Isolated DNA Compounds. Congress is aware of these subject matter eligibility issues: While it has failed to pass legislation that would have excluded human genes or gene sequences from patent-eligibility, it recently enacted provisions excluding claims directed to or encompassing a "human organism" and directing the PTO to study ways to provide genetic testing where patents on genes and genetic testing exist. Compare Life Patenting Moratorium Act of 1993, S. 387, 103d Cong. § 3 (1993), with Leahy-Smith America Invents Act, Pub. L. No. 112-29, §§ 27, 33, 125 Stat. 284, 338-340 (2011). Consequently, the Court should "decline to narrow the reach of § 101 where Congress has given no indication that it intends this result." *J.E.M. Ag Supply*, 534 U.S. at 144-146 (declining to exclude plants from patent eligibility where, among other things the PTO had issued utility patents for plants for 16 years without action from Congress); cf. *Microsoft Corp.* v. *i4i Ltd. P'ship*, 131 S. Ct. 2238, 2252 (2011) (where Congress has "allowed the Federal Circuit's * * * interpretation of § 282 [of the Patent Act] to stand," "[a]ny re-calibration of the standard of proof remains in its hands").

Moreover, the biotechnology industry has substantially relied on this Court's precedent—and more directly the PTO's policy—to seek and obtain patent claims to Isolated DNA Compounds. As of 2006, there were approximately 33,000 issued patents claiming nucleic acids. National Research Council, *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation and Public Health* 101 (Stephen A. Merrill & Ann-Marie Mazza eds., National Academies Press, 2006). There are many more such patents today. Those patents help protect the significant investment needed to develop and obtain regulatory approval for new products in the biotechnology industry. See, *e.g.*, Federal Trade Commission Report, *Emerging Health Care Issues: Follow-on Biologic Drug Competition*, 30, 47 (June 2009) (concluding that "[p]atent protection fuels the biotechnology industry's R&D engine" and is "necessary to attract the capital to fund high-risk investment"); Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 Managerial and Decision Econ. 469, 475 (2007) (estimating that the development costs for new biologic-based therapeutics to be in excess of one billion dollars for each approved molecule). Dramatic shifts in the scope of patentable subject matter would unfairly undercut these investments and upset the reasonable expectations and needs of inventors who have acted against the backdrop of long-standing precedent interpreting § 101 broadly and incrementally. See *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002) ("[C]ourts must be cautious before adopting changes that disrupt the settled expectations of the investing community").

For these reasons, the ABA endorses this Court's traditional practice of incrementally developing its jurisprudence for determining patent-eligible subject matter on a claim-by-claim basis. That consistent approach allows practitioners to reliably advise clients on the patent-eligibility of new technologies in the context of a stable regulatory framework and avoids dramatic shifts in the definition of patent-eligible subject matter, such as a *per se* disqualification of Isolated DNA Compounds, which would upset reasonable investment-backed expectations and undercut innovation in the important field of biotechnology.

II. Under the Applicable Precedent, Isolated DNA Compounds Are Patent-Eligible Subject Matter Because They Are Not Products of Nature.

This Court granted the Association for Molecular Pathology's earlier petition and remanded for further consideration in light of the intervening decision in *Mayo*. See *Ass'n for Molecular Pathology* v. *Myriad Genetics, Inc.*, 132 S. Ct. 1794 (2012). On remand, the Federal Circuit correctly determined that *Chakrabarty*, not *Mayo*, controls the question of patent-eligibility for the composition claims at issue here. *Ass'n for Molecular Pathology* v. *U.S. Patent & Trademark Off.*, 689 F.3d 1303, 1325-1327 (Fed. Cir. 2012) ("*Myriad II*"). Under *Chakrabarty*, Isolated DNA Compounds are patent-eligible subject matter because they are not products of nature.

A. *Chakrabarty*, Not *Mayo*, Controls the Patent-Eligibility of Isolated DNA Compounds.

This Court's decision in *Mayo* requires no change to its earlier precedents governing the analysis of the patent-eligibility of compositions. The claims at issue in *Mayo* were process claims reciting a law of nature, namely the relationship between the concentration of a drug metabolite in the blood and the efficacy of the drug. *Mayo*, 132 S. Ct. at 1296. Consequently, the sole question there was whether the challenged claims "add[ed] *enough*" to their statement of this natural relationship "to qualify as patent-eligible processes that *apply* natural laws." *Id.* at 1297 (emphasis in original).

In contrast, the composition of matter claims at issue here do not recite a law of nature, nor do they claim the application of one. Indeed, they are drawn to a different class of statutory subject matter, "composition of matter," than were the process claims in *Mayo*. 35 U.S.C. § 101. The relevant question for the patent-eligibility of these composition claims is whether the claimed Isolated DNA Compounds are "nature's handiwork" or rather a patent-eligible, human-made invention. See *Chakrabarty*, 447 U.S. at 309-310; *id.* at 313 (noting from the legislative history of § 101 that "the relevant distinction was * * * between products of nature * * * and human-made inventions"). *Mayo* did not address this question, much less purport to change how such claims are analyzed for eligibility under § 101.

Nor does the analysis in *Mayo* inform the determination whether the claimed DNA compounds exist in nature or are human-made inventions.

Adding merely "conventional or obvious [pre]-solution activity" is ordinarily not "sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law." *Mayo*, 132 S. Ct. at 1298 (quoting *Parker* v. *Flook*, 437 U.S. 584, 590 (1978) (alterations in *Mayo*)). But that inquiry is irrelevant to whether a composition is a product of nature. There is no reason to treat the patent-eligibility of Isolated DNA Compounds differently from any other chemical compound derived from a natural material or source.

B. Isolated DNA Compounds Are Patent-Eligible Because They Are Not Products of Nature.

As the Federal Circuit recognized, the claimed Isolated DNA Compounds at issue in this case are human-made, "free-standing" molecules that are markedly different in character from anything found in nature. See *Myriad II*, 689 F.3d at 1328. Under this Court's applicable precedent, Isolated DNA Compounds—from humans or any other organisms—are therefore patent-eligible subject matter. *Chakrabarty*, 447 U.S. at 309-310.

To be sure, some of the compositions claimed by Myriad correspond to portions of larger compounds that are found in nature—human chromosomes—but the claimed compositions meaningfully differ from those naturally occurring compounds. Most significantly, the Isolated DNA Compounds claimed by Myriad are distinct chemical structures that correspond to only a small fraction of a chromosome[4] and are created by human intervention, either by synthesis *de novo* or by cleavage from a chromosome. See *Myriad II*, 689 F.3d at 1328; Utility Examination Guidelines, 66 Fed. Reg. at 1093 ("The [human] body does not contain the patented, isolated and purified gene because genes in the body are not in the patented, isolated and purified form."). Although petitioners liken this to "isolating" a kidney from a human body or "isolating" leaves from trees, Pet'r Br. at 2, an intact organ or a leaf is not a distinct composition of matter or article of manufacture in the way molecules synthesized or cleaved from a chromosome are. The molecules, which are distinct chemical compositions that have been identified, located, and extracted (or synthesized) through human ingenuity, meaningfully differ from what occurs in nature in a way that an "isolated" intact organ or leaf simply does not.

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[4] A chromosome might include lengths of over a hundred million base pairs of DNA, while the *BRCA1* and *BRCA2* genes at issue here are only approximately 80,000 base pairs long.

More specifically, as distinct chemical structures, Isolated DNA Compounds have utility beyond that of their related, naturally occurring molecules. Petitioners' brief describes the unique usefulness of Myriad's claimed Isolated DNA Compounds for, among other things, genetic testing, therapeutics, biomedical devices and sequencing technologies. See, *e.g.*, Pet'r Br. at 44-45. This Court has relied on such acquired utility to distinguish between claims drawn merely to some patent-ineligible "handiwork of nature" and claims drawn to a patent-eligible manufacture or composition. Compare *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 131-132 (1948), with *Chakrabarty*, 447 U.S. at 309-310.

Myriad II, 689 F.3d at 1328.

Other of Myriad's claimed compositions do not even correspond to any naturally occurring DNA molecule. cDNA molecules lack certain non-coding sequences, termed introns, that are found in the naturally occurring chromosome, and thus, relative to a chromosome, cDNA molecules have been further edited and recombined to create a molecule that does not exist in nature. See *Myriad II*, 689 F.3d at 1329. Accordingly, claims to such Isolated DNA Compounds do not implicate any naturally occurring DNA molecule found in any living organism, human or otherwise.

Claims to Isolated DNA Compounds are thus "not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity 'having a distinctive name, character and use.'" *Chakrabarty*, 447 U.S. at 309-310 (quoting *Hartranft* v. *Wiegmann*, 121 U.S. 609, 615 (1887)). And under this Court's longstanding precedent, such subject matter is patent-eligible under § 101. *Id.*

C. Claims to Isolated DNA Compounds Neither Claim Nor "Tie Up" Laws of Nature.

Even if the biological information communicated by the sequence of nucleotides in an Isolated DNA Compound could be considered a "law of nature," that Isolated DNA Compound is nonetheless eligible for patent protection. "While a scientific truth * * * is not [a] patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be." *Mackay Radio & Tel. Co. v. Radio Corp. of Am.*, 306 U.S. 86, 94 (1939). Unlike the process claimed in *Mayo*, which "amount[ed] to nothing significantly more than an instruction to doctors to apply the applicable laws [of nature] when treating their patients," a claim to an Isolated DNA Compound does not monopolize or otherwise prohibit the use of the underlying biological sequence information. *Mayo*, 132 S. Ct. at 1297-1298. Instead, such composition claims prevent the use of only their physical embodiments, *i.e.*, the non-naturally occurring, tangible compositions within the scope of the claims. 35 U.S.C. § 271 (precluding, among other things, making or using the "patented invention"); see also *Microsoft Corp.* v. *AT & T Corp.*, 550 U.S. 437, 449 (2007) (distinguishing between abstract ideas and physical embodiments). The intangible sequence information is therefore not "tied up" by the composition claim. See *Mahn* v. *Harwood*, 112 U.S. 354, 361 (1884) ("The public has the undoubted right to use, and it is to be presumed does use, what is not specifically claimed in the patent."). Indeed, Myriad's claims to "comparing" or "analyzing" the underlying sequence information were held patent-ineligible by the Federal Circuit. *Myriad II*, 689 F.3d at 1334-1335.

Thus, scientists are free to use the sequence information in Myriad's Isolated DNA Compounds, as well as the knowledge of a correlation between mutations in that sequence with the risk of developing breast cancer, to make further discoveries without making or using the claimed Isolated DNA Compounds. Indeed, the *BRCA1* and *BRCA2* cDNA sequences have been included in public biological sequence databases for nearly two decades. See GenBank Accession No. U14680 (*BRCA1*), *available at* http://www.ncbi.nlm.nih.gov/nuccore/555931 and GenBank Accession No. U43746 (*BRCA2*), *available at* http://www.ncbi.nlm.nih.gov/nuccore/U43746; see also U.S. Pat. No. 5,747,282, col. 53, ll. 7-9. Those databases are used hundreds of thousands of times a day by scientists around the world to analyze and compare biological sequence information. See, *e.g.*, Dennis A. Benson *et al.*, *GenBank*, 41 Nucleic Acids Research D36 (2013); *Database Resources of the National Center for Biotechnology Information*, 41 Nucleic Acids Research D8 (2013); James Ostell, *Databases of Discovery*, 3 ACM Queue 40 (2005). Such computer-based analysis of biological sequence information has revolutionized life sciences research, underpinning a broad range of inquiry, from the study of the evolutionary relationships among organisms to the identification of the function of new genetic sequences. See, *e.g.*, Minoru Kanehisa & Peer Bork, *Bioinformatics in the Post-Sequence Era*, 33 Nature Genetics 305 (2003); Kenneth H. Wolfe & Wen-Hsiung Li, *Molecular Evolution Meets the Genomics Revolution*, 33 Nature Genetics 255 (2003). And with respect to the diagnostic screening of the BRCA genes at issue here, once a BRCA sequence has been determined, that sequence information may be freely analyzed for mutations correlating with a risk for developing cancer. *Myriad II*, 689 F.3d at 1334-1335. Composition claims to Isolated DNA Compounds therefore do not "tie up" the use of biological sequence information in a way that would "inhibit future innovation premised upon" the biological sequence information in the patent. *Mayo*, 132 S. Ct. at 1301-1302.

That Myriad's composition claims might, given the current state of the art,[5] effectively grant it exclusive rights to the determination of the particular sequence of an individual's BRCA genes—even when that information might have medical significance—reflects the normal operation of patent law, granting the inventor of a human-made molecule certain temporary rights in an effort to encourage the useful arts. Patents are routinely awarded for life-saving technologies such as pharmaceuticals and medical devices. Whether the practical implications of patent protection warrant making an exception to ordinary rules in an emerging area of technology presents a quintessential question of policy that this Court has traditionally left for Congress. And with respect to subject matter eligibility in particular, this Court has consistently refrained from categorically excluding subject matter from § 101 on the basis of such policy considerations. See *supra* at 6-7. Cf. *Gottschalk* v. *Benson*, 409 U.S. 63, 72-73 (1972) (declining to alter the bounds of § 101 where "[t]he technological problems tendered in the many briefs before us indicate to us that considered action by the Congress is needed."); *Mayo*, 132 S. Ct. at 1304-1305.

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[5] Conventional sequencing approaches for a single gene typically involve making or using "isolated" versions of the gene, implicating patent claims to the corresponding Isolated DNA

Compound. In the past several years, however, new sequencing approaches have been developed that avoid using Isolated DNA Compounds. Employing those approaches, one might be able to sequence a BRCA gene and analyze it without running afoul of any of Myriad's patent claims. See Christopher M. Holman, *Debunking the Myth that Whole-Genome Sequencing Infringes Thousands of Gene Patents*, 30 Nature Biotechnology 240, 241 (2012); W. Nicholson Price II, *Unblocked Future: Why Gene Patents Won't Hinder Whole-Genome Sequencing and Personalized Medicine*, 33 Cardozo L. Rev. 1601, 1606 (2012).

III. Subject Matter Eligibility under 35 U.S.C. § 101 Is Separate and Distinct from the Other Requirements for Patentability.

Finally, the analysis of whether claimed subject matter is *eligible* for patent protection should not import any of the additional, separate requirements for the issuance of a patent. In *Mayo*, the Court remarked, in dicta, that the patent-eligibility inquiry of § 101 "might sometimes overlap" with the novelty inquiry of § 102. 132 S. Ct. at 1304. That commentary sparked concern among practitioners that the Court was departing from its longstanding precedent that the other requirements for patentability, *e.g.*, novelty and obviousness, are not relevant to patent-eligibility analysis. See, *e.g.*, Jeffrey Fox, *Industry Reels as* Prometheus *Falls and* Myriad *Faces Further Reviews*, 30 Nature Biotechnology 373 (2012); Tamsen Valoir, Mayo v. Prometheus: *Natural Law or Mental Step*, 24 Intell. Prop. & Tech. L. J. 3, 5 (2012).

As noted above, *Mayo* dealt with whether the method claims there constituted a patent-eligible application of a law of nature. The Court consequently examined whether the claimed method added anything more than insignificant, "conventional or obvious" pre-solution activity "sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law." *Mayo*, 132 S. Ct. at 1298. *Mayo* did not, therefore, import novelty into its patent-eligibility analysis generally.

Indeed, this Court has previously explained that patent-eligibility under § 101 is separate and distinct from the successive requirements for patentability in the Patent Statute. Section 101 "is only a threshold test" and patent-eligible subject matter "must also satisfy 'the conditions and requirements of this title' * * * includ[ing] that the invention be novel, see § 102, nonobvious, see § 103, and fully and particularly described, see § 112." *Bilski*, 130 S. Ct. at 3225 (quoting 35 U.S.C. § 101); see also *Flook*, 437 U.S. at 593 ("The obligation to determine what type of discovery is sought to be patented must precede the determination of whether that discovery is, in fact, new or obvious."). Further, notwithstanding the words "new and useful" in § 101, novelty is not "an appropriate consideration under § 101" and "*is of no relevance* in determining whether the subject matter of a claim falls within the § 101 categories of possibly patentable subject matter." *Diamond* v. *Diehr*, 450 U.S. 175, 188-189 (1981) (emphasis added); *id.* at 190 ("The question therefore of whether a particular invention is novel is wholly apart from whether the invention falls into a category of statutory subject matter.") (internal quotation marks omitted); *Flook*, 437 U.S. at 588 (explaining that subject matter eligibility under § 101 "does not involve the familiar issues of novelty and obviousness"); see also *Kewanee Oil Co.* v. *Bicron Corp.*, 416 U.S. 470, 483 (1974) ("no patent is available for a discovery, however useful, novel, and nonobvious, unless it falls within one of the express categories of patentable subject matter of 35 U.S.C. § 101").

That subject matter eligibility is separate and distinct from novelty and non-obviousness follows from the fact that the requirements are set out as separate and distinct statutory provisions. This "statutory scheme" establishes, in the words of Judge Giles S. Rich, one of the drafters of the Patent Act of 1952, "three doors" that must be opened by inventors.

Section 101 is the "first door" and inquires "[w]hat kind of invention or discovery" the inventor seeks to patent. *In re Bergy*, 596 F.2d 952, 960 (C.C.P.A. 1979) (Rich, J.), *aff'd, sub nom. Diamond* v. *Chakrabarty*, 447 U.S. 303 (1980). Only if the invention "falls into any one of the named categories" in § 101, is the inventor "allowed to pass through to the second door," novelty, and then onto the "third door," non-obviousness. *Id.* at 960-961.

The ABA thus endorses the principle that the inquiry into subject matter eligibility under § 101 is a separate and distinct requirement from, and should be resolved independently of, the additional conditions and requirements for obtaining a patent set out in §§ 102, 103 and 112. Consequently, with respect to Myriad's claims here, petitioners' assertion that the techniques Myriad used to create its claimed Isolated DNA Compounds were well-known, routine or conventional at the time of invention, Pet'r Br. at 37, is irrelevant to whether that subject matter is patent-eligible. Likewise irrelevant are petitioners' assertions that the scope of Myriad's claims encompass subject matter beyond what Myriad invented and described in its application, Pet'r Br. at 11-17, 37. Those concerns may implicate other statutory conditions and requirements for the issuance of a patent, specifically, that the invention be novel (§ 102); nonobvious (§ 103); and fully described and enabled (§ 112). But the only question here is whether Myriad's claimed compositions are "products of nature" or "humanmade inventions." *J.E.M. Ag Supply*, 534 U.S. at 134 (quoting *Chakrabarty*, 447 U.S. at 313).

CONCLUSION

For the reasons set out above, the ABA respectfully requests that this Court hold that Isolated DNA Compounds, including those corresponding to genes from humans or other organisms, are patent-eligible subject matter. The judgment should be affirmed.

Respectfully submitted.

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MARCH 14, 2013

APPENDIX A

AMERICAN BAR ASSOCIATION

ADOPTED BY THE HOUSE OF DELEGATES

FEBRUARY 14, 2011

RESOLUTION 111

RESOLVED, That the American Bar Association supports the continued recognition of judicially-created exceptions to patent eligibility for laws of nature, abstract ideas, or physical phenomena under 35 U.S.C. § 101, and the continued reliance on the separate statutory requirements for patentability under 35 U.S.C. §§ 102 and 103 for novelty and non-obviousness.

FURTHER RESOLVED, That the American Bar Association supports application of standards used in assessing patent eligibility under the provisions of 35 U.S.C. § 101 in a non-discriminatory manner that treats isolated DNA compounds no differently from other materials that are derived from or otherwise relate to natural materials or sources.

FURTHER RESOLVED, That the American Bar Association opposes per se disqualification from patent eligibility under 35 U.S.C. § 101 of isolated DNA compounds that do not occur in nature in their isolated forms.

FURTHER RESOLVED, That the American Bar Association opposes the adoption of any "products of nature" doctrine that would automatically require the exclusion of isolated DNA compounds from patent eligibility as "products of nature."

REPORT

Scientific advances in the use of DNA technology for diagnosis and treatment of disease have contributed substantially and measurably to improvements in human health, quality of life, and longevity. For more than two decades, our government has recognized these realities, and has appropriately provided incentives for continued advances in a number of ways, including financial support for further research and development, and patent protection for new inventions.

A fundamental challenge to the eligibility of any and all DNA technology to be considered for patenting is underway. One federal court has ruled that such technology is categorically ineligible, and that ruling is under appeal in the U.S. Court of Appeals for the Federal Circuit. Regardless of the outcome in that proceeding, in view of the importance and notoriety of this litigation, review by the full en banc Federal Circuit or further appeal to the Supreme Court of the United States is a distinct possibility.

Congress has also shown interest in the issue, as demonstrated by the introduction of legislation that would provide a statutory ban on patenting of DNA technology.

This resolution asks the House of Delegates to approve policy to express ABA opposition to the damaging reversal of policy called for by the District Court decision, and to support Association participation in further proceeding to resolve this issue.

A. The *Myriad* Case: Summary and Overview

In *Association for Molecular Pathology v. United States Patent and Trademark Office*, 2010 U.S. Dist. LEXIS 35418 (S.D.N.Y. Apr. 2, 2010) ("*Myriad*"), a critical issue before the court was whether an isolated DNA compound, which does not appear in nature in that form, qualifies as subject matter eligible for patenting under 35 U.S.C. section 101.[1] *Id.* at 3. The *Myriad* court held that it does not. *Id.* The court notes that subject matter is patent eligible if it is "markedly different" from a product of nature and then proceeds to find that isolated DNA was not markedly different because it is not "sufficiently distinct in its fundamental characteristics" from the corresponding DNA sequence found in nature. *Id.* at 144-145.

The *Myriad* court erred in its interpretation of section 101 and specifically in its application of the test for patent eligibility. Patent eligibility under the statute is broad, and the Supreme Court's precedents provide only three specific exceptions to those broad eligibility principles. Inventions seeking to capture laws of nature, physical phenomena, or abstract ideas may not be patented. While the Section does not believe that the "markedly different" test applied by the court is appropriate for determining patent eligibility, the isolated DNA compound at issue in *Myriad* was, in fact, markedly different from what occurs in nature. It does not fall under any of the narrow exceptions to the wide scope of section 101 that have been articulated by the Supreme Court.

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[1] The requirements of Section 101 only serve as a threshold to consideration of the requirements that must be satisfied under Sections 102 (novelty), 103 (non-obviousness) and numerous other provisions of the Patent Act in order for any invention to be patentable or patented, Those requirements of patentability were not considered by the *Myriad* court and thus not determined or covered by the court's decision on summary judgment. An isolated DNA compound that meets the threshold requirements of Section 101 might not be patentable for failure to meet one or more of the patentability requirements.

The isolated DNA compound claimed in the Myriad patent is a chemical compound. Moreover, in the isolated form that is claimed, it does not occur in nature and is not merely purified from natural DNA.

The isolated DNA compounds claimed in the Myriad patents are isolated forms of a gene called the "BRCA" gene. Through sophisticated research, the inventors discovered that mutations in the BRCA genes (*i.e.*, small, inheritable, individual-to-individual variations of the sequences of the DNA building blocks making up the BRCA genes) correlate with a woman's risk of developing breast cancer. Thus, the isolated DNA claimed in the patents has become a useful tool for doctors to use to assess a woman's risk of breast cancer and provides valuable diagnostic and prognostic information which assists in selecting treatment options.

The BRCA gene is one of more than 20,000 genes that exist in the human genome. The genes exist in the nucleus of each cell on long strands of DNA called "chromosomes." Each chromosome consists of thousands of genes in which the DNA exists in a complex structure with proteins. The human genome consists of forty-six chromosomes. Thus, in its natural environment, the BRCA gene is a small part of a long strand of DNA existing on one of forty-six chromosomes. Each chromosome consists of millions of the DNA building blocks (called "nucleotides,") which, in turn, are contained in the cell nuclei. The cell is a complex milieu of enzymes and numerous other proteins, lipids, carbohydrates, salts and nucleic acids. The cells form the tissues of the human organism.

The isolated DNA claimed in the Myriad patents is a chemical compound that has been identified and excised from the chromosome. It is separated from all of the components of the chromosome, the nucleus, the cell and the tissue. In its isolated form, it is useful in diagnostic and prognostic procedures designed to ensure people's health and well being. In contrast, the DNA in its natural form, as it exists in tissues, cells and chromosomes, has no value in such diagnostic and prognostic procedures.

There can be no serious dispute that the isolated DNA compounds claimed in the Myriad patents are compositions of matter that did not occur in nature. They are the product of human ingenuity and intervention; they are man-made. They have a utility that the DNA in its complex natural environment does not have.

Isolated DNA compounds are not merely the product of purification. Isolating DNA entails, inter alia, a chemical re-arrangement -- breaking the covalent chemical bonds of chromosomal DNA to form a new chemical structure not found in nature. While isolated DNA may be derived from natural DNA, it is indisputably a man-made compound not found in nature and not purified from its natural environment. The claimed isolated DNA compound is a product of man, not nature.

The patent statute defines patent-eligible subject matter broadly to meet the Constitutional mandate to "promote the progress of science and the useful arts by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries." U.S. Constitution, Art. I, §8, cl. 8. A primary purpose of the patent system is to provide incentives for investment into research that enhances the quality of life and economic vitality of the country.

Although the Myriad court acknowledged the chemical distinctions between the claimed isolated DNA and the naturally occurring substance, the court found that such compositions of matter are not subject matter eligible for patent protection because the isolated DNA was not "markedly different" from natural DNA.:

B. 35 U.S.C. Section 101 and Its Scope

Section 101 defines the subject matter eligible for patenting under the Patent Act:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Section 101 thus specifies four independent categories of inventions or discoveries that are eligible for patent protection: processes, machines, manufactures, and compositions of matter. "In choosing such expansive terms . . . modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope." *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980). Congress took this permissive approach to patent eligibility to ensure that "'ingenuity should receive a liberal encouragement.'" *Id.* at 308-309 (quoting 5 Writings of Thomas Jefferson 75-76 (H. Washington ed. 1871)).

The Supreme Court's precedents provide three specific exceptions to section 101's broad patent-eligibility principles: laws of nature, physical phenomena, and abstract ideas. *Chakrabarty*, 447 U.S. at 309. A naturally occurring substance that has been isolated into a new and useful form not found in nature is a "composition of matter" that does not fall within the narrow exceptions to patent eligibility that have been identified by the Supreme Court. *Id.* at 310.

However, the exceptions to patentable subject matter should not be confused with the remaining requirements for patentability, particularly the requirement that the invention not be obvious.

Bilski v. Kappos, 561 U. S. ____ (2010) at pages 5, 12-13 of the slip opinion. Thus, while a composition of matter may qualify as patent-eligible subject matter under section 101, what appears in nature may still render the composition of matter unpatentable as anticipated or obvious. Section 101 is a threshold requirement to define the subject matter that is eligible for patenting. Other sections define whether that subject matter is worthy of a patent.

C. Isolated DNA Constitutes Patent Eligible Subject Matter under Section 101

An isolated DNA sequence qualifies as a "composition of matter" under section 101. A "composition of matter" includes "all compositions of two or more substances and . . . all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids." *Chakrabarty,* 447 U.S. at 309. An "isolated DNA sequence" constitutes a "composition of two or more substances" by definition, which the *Myriad* court provided in construing that term:

> "Isolated DNA" is therefore construed to refer to a segment of DNA nucleotides existing separate from other cellular components normally associated with native DNA, including proteins and other DNA sequences comprising the remainder of the genome, and includes both DNA originating from a cell as well as DNA synthesized through chemical or heterologous biological means.

Myriad at 99.

The isolated DNA sequence in *Myriad* also falls outside the Supreme Court's three limited exceptions to patentable subject matter: laws of nature, physical phenomena, and abstract ideas. *Chakrabarty,* 447 U.S. at 309. Accordingly, it is patent-eligible subject matter.

D. The *Myriad* Court Erred in its Application of a "Markedly Different" Test for Patent Eligibility

In *Chakrabarty*, the Supreme Court distinguished its earlier decision in *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948) by observing that, unlike the mixture of natural microbial cultures claimed in *Funk Bros.*, Chakrabarty's genetically engineered microorganism had "markedly different characteristics from any found in nature and [was] one having the potential for significant utility." 447 U.S. at 310. The *Myriad* court extrapolated from this language a conclusion that the Supreme Court's test for patent eligibility required that the claimed composition be "markedly different" from what occurs in nature. However, in distinguishing the nature of Chakrabarty's invention from that at issue in *Funk Bros.*, the Supreme Court did not hold that "markedly different" was a substantive requirement for patent eligibility. In fact, the Court emphasized in that case that Congress defined patent eligibility broadly, and "in choosing such expansive terms as 'manufacture' and 'composition of matter,' modified by the comprehensive 'any,' Congress plainly contemplates that the patent laws would be given wide scope." 444 U.S. at 308-09.

By reading a "markedly different" requirement into section 101, the *Myriad* court interjects a nonobviousness requirement into the test for patent eligibility. But, in *Chakrabarty*, the Supreme Court made clear that the requirements of nonobviousness and novelty are distinct from patent eligibility under section 101. *Id.* n.5. Instead, the Supreme Court focused on the statutory categories of invention "manufacture" and "composition of matter" and held that inventions falling within those broad categories, as opposed to "laws of nature, physical phenomena, [or] abstract ideas" are eligible for patenting. 447 U.S. at 310. Once an invention is shown to satisfy these broad threshold requirements for patent eligibility, its differences from the prior art — including what occurs in nature — are assessed to determine if the statutory requirements of novelty and nonobviousness are satisfied under sections 102 and 103.

As noted by the United States Court of Customs and Patent Appeals, there are no extraordinary criteria apart from section 102 for determining whether subject matter is "new" under section 101:

> The criteria for determining whether a given subject matter is "new" within the meaning of section 101 are no different than the criteria for determining whether the subject matter possesses the "novelty" expressed in the title of section 102. The word "new" in section 101 is defined and is to be construed in accordance with the provisions of section 102."

In re Bergstrom, 427 F.2d 1394, 1401 (C.C.P.A. 1970). Thus, the interpretation of "markedly different" in Chakrabarty is not properly read to establish a new test for patent-eligibility. Rather, "markedly different" must be understood in the context of the statutory framework. A composition of matter is sufficiently different from the natural substance if it is new under section 102.

Courts have upheld patents that claim a composition of matter derived from, or otherwise related to, natural materials and meet the statutory criteria of being new and unobvious. *See, e.g., Merck v. Olin Mathieson Chemical Corporation*, 253 F.2d 156 (4th Cir. 1958). Compositions that have been held to be unpatentable "products of nature" are not new. *Id.* at 162. There is no statutory basis, and it is unnecessary to extend any concept of subject matter being "markedly different" beyond section 102. The test for whether subject matter is markedly different is wholly defined by statute.

The *Myriad* court, however, instead required the following more stringent standard for defining whether subject matter is markedly different:

> There will almost inevitably be some identifiable differences between a claimed invention and a product of nature; the appropriate section 101 inquiry is whether, considering the claimed invention as a whole, it is sufficiently distinct in its fundamental characteristics from natural phenomena to possess the required 'distinctive name, character, [and] use.'

Myriad at 137-138 (quoting *Chakrabarty*, 447 U.S. at 309-10) (emphasis added). Ultimately, in view of its finding that DNA is a 'physical embodiment of information,' the *Myriad* court declared the chemical difference between native DNA and isolated DNA to be insufficient to meet the standard.

E. Claims to Isolated DNA are Claims to Chemical Compounds Not to Information

The Myriad court is correct that DNA communicates biological information when it noted that "DNA, and in particular the ordering of its nucleotides, therefore serves as the physical embodiment of laws of nature — those that define the construction of the human body." *Myriad* at 135. However, to the extent DNA communicates information, the information embodied in the DNA sequence is not part of the claimed (patented) composition. That is, the sequence information could be and is freely usable - to upload into a computer, to study similarities or differences with other genes, to understand mutations in some populations, and to make new discoveries and inventions. A claim to the chemical composition - a physical embodiment - does not prohibit the use of the scientific information that is communicated by the sequence data. The information aspect of a claim to isolated DNA is dedicated to the public once the patent published. Accordingly, that DNA uniquely communicates biological information has little, if any, bearing on whether isolated DNA compounds are patent eligible subject matter under section 101.

F. The ABA Should Oppose Application of any "Products of Nature" Doctrine That Would Have the Effect of Producing a Subject Matter Exclusion From Patent Eligibility for Isolated DNA Compounds

The Myriad court supports its holding in its interpretation of the so-called "product of nature" doctrine. The origins and boundaries of this doctrine are debatable, particularly to the extent the "product of nature" doctrine defines patent eligibility rather than the old standard of "invention" in what is now embodied under sections 102 and 103. However, the ABA should oppose application of any "product of nature" doctrine that categorically excludes isolated DNA compounds from patent eligibility.

In *Am. Fruit Growers, Inc. v. Brodgex Co.*, 283 U.S. 1 (1931), the Supreme Court held that fruit whose skin had been treated with mold-resistant borax did not constitute a patentable article of "manufacture." *Id.* at 11-12. The Court focused on the word "manufacture" and found that there must be a "transformation; a new and different article must emerge having a distinctive name, character, or use." *Id.* at 13. The court noted that the borax-coated orange is patent-ineligible because it "remains a fresh orange, fit only for the same beneficial uses as theretofore." *Id.* at 12. However, the issue in *Myriad* was whether an isolated DNA sequence constituted a "composition of matter" and fell outside the limited exceptions to section 101. The issue was not whether the isolated

DNA sequence also constituted a patentable article of manufacture. *Am. Fruit Growers* is thus inapposite to the issue in *Myriad*. Furthermore, as previously noted, isolated DNA compounds are no way found in nature and as a new chemical composition are different than natural chromosomal DNA. Thus, *Am. Fruit Growers* would not support the exclusion of isolated DNA compounds from patent eligibility.

In *Funk Bros.*, the Supreme Court held that a claim directed to a plurality of naturally-occurring bacterial strains that did not inhibit each other was invalid. *Id.* at 131-32. The Court found that the aggregation of naturally-occurring strains, which did not exhibit characteristics different from the individual strains themselves, "was not the product of invention." *Id.* at 132. This holding must be understood in the context of the pre-1952 statute, where "invention" was not statutorily defined, but rather it was a judicially applied test of what is now obviousness under section 103. Accordingly, the holding of the Court cannot be read as precluding patents to "products of nature" generally as ineligible subject matter; rather, products of nature that are not unobvious are unpatentable. However, even if the holding could be fairly interpreted to define patent eligibility of subject matter rather than patentability, it is clear that the Court merely required that the aggregation of strains exhibit some characteristic different from the individual strains themselves. *Id.* Accordingly, *Funk Bros.* also does not support excluding isolated DNA compounds from patent eligibility.

In *Chakrabarty*, discussed above, the Supreme Court found that a live, human-made micro-organism constituted patent eligible subject matter because it had "markedly different" characteristics from what appeared in nature. *Chakrabarty*, 447 U.S. at 310. It was unnecessary for the Court in *Chakrabarty* to further define "markedly different" as being new under section 102 because that issue was not before the Court. However, the Supreme Court in *Chakrabarty* plainly did not articulate a new test for patent eligibility that the subject matter must be different more broadly than being new under section 102.

In *The American Wood-Paper Co. v. The Fibre Disintegrating Co.*, 90 U.S. (23 Wall.) 566, 593-94 (1874), the Supreme Court held that a purified product was not patentable merely because it was purified from a new source, when it had already been purified from another source. It was not new. The Court observed:

> There are many things well known and valuable in medicine or in the arts which may be extracted from diverse substances. But the extract is the same, no matter from what it has been taken. A process to obtain it from a subject from which it has never been taken may be the creature of invention, but the thing itself when obtained cannot be called a new manufacture.

Id. at 593-94. The Supreme Court suggested, however, that if the purified product had been purified for the first time, it would qualify as patent-eligible subject matter. *Id.* at 594. The *Myriad* court, however, misapplied *American Wood-Paper* in two respects — it confused patent eligibility with being new (novelty) and it also equated purifying a product from a natural source with chemically deriving isolated DNA from its chromosomal DNA. As previously noted, deriving isolated DNA entails chemical modifications to chromosomal DNA such that a new compound — not anywhere found in nature — is produced.

In *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 311 (1884), the Supreme Court rejected a patent on an artificial version of a natural, well-known dye called alizarine. The artificial version and the natural version were identical except in name. *Id.* Even assuming the Court was addressing patent eligibility as opposed to novelty, which is unclear from the record, the Court merely found that an invention that differed from a product of nature only in name could not be patented. *Id.*

Although the *Myriad* court also cited very old lower court decisions for support of its finding that isolated DNA compounds were ineligible subject matter as a "product of nature," those decisions, to the extent they contradict the Supreme Court's expansive interpretation of section 101 in *Chakrabarty*, are no longer good law. *See, e.g. Myriad* at *38 (citing *Gen. Elec. Co. v. De Forest Radio Co.*, 28 F.2d 641 (3d Cir. 1928); *In re Marden*, 47 F.2d 957 (C.C.P.A. 1931); and *In re Marden*, 47 F.2d 958 (C.C.P.A. 1931)). Furthermore, each also finds the "product of nature" unpatentable (in contrast to being patent ineligible) when the requirements under the Patent Act are not otherwise met. That is, the claimed subject matter is not novel or unobvious under sections 102 and 103. A finding of subject matter being "unpatentable" confuses patent eligibility of the subject matter and patentability. *See Merck*, 253 F.2d at 162. The cited cases also provide claims to elements, which are not compositions under section 101 and therefore may also be readily distinguished. *See Chakrabarty*, 447 U.S. at 309 which defines the term "composition" under the act as including "all compositions of two or more substances and . . . all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids." Accordingly, none of the decisions cited by Myriad support the proposition that isolated DNA should be placed in a category of patent-ineligible subject matter as a so-called "product of nature." Indeed, the ABA should oppose any such categorization as not being proper.

G. The IPL Section Supports the Application of Standards Used in Assessing Patent Eligibility under the Provisions of 35 U.S.C. Section 101 in a Non-discriminatory Manner

The standards used in assessing patent eligibility under the provisions of 35 U.S.C. 101 must be applied non-discriminatory manner that treats isolated DNA compounds no differently from other materials that are derived from or otherwise relate to natural materials or sources. The practical impact of the *Myriad* court's holding is that the isolated DNA is treated differently than other chemicals that may be derived from natural sources, such as proteins from biologic sources, antibiotics isolated from natural sources, microorganisms, or petroleum-based products. A claim for a particular isolated DNA compound, such as BRCA1 or BRCA2, should be subjected to the requirements for patentability under sections 101, 102 and 103. By creating a blanket subject matter exclusion for all isolated DNA compounds, the *Myriad* court would preclude full 101, 102 and 103 analysis and deprive of patent protection all those future inventions of isolated DNA compounds that meet the requirements of 102 and 103.

The IPL Section has long opposed application of the patent law in a manner that discriminates by subject matter and the ABA has adopted policy similarly opposing unduly restrictive judicial interpretation of patent eligibility under section 101. Most recent of these is the policy adopted by the House of Delegates at the 2009 Annual Meeting, expressing opposition to an unduly restrictive ruling by the Federal Circuit on patent eligibility under section 101. In its July 2010 decision in *Bilski v. Kappos*, the U.S. Supreme Court issued a decision in accord with that taken in an ABA amicus brief, and rejected the narrow standard for patent eligibility formulated by the Federal Circuit.

H. Patent Eligibility of Isolated DNA is Good Patent Policy

The publicity around the *Myriad* case has spurred considerable debate on the merits of patenting isolated DNA. This debate is generally summarized by the *Myriad* court. *Myriad*, at 71-83. One aspect of the debate is whether patents to isolated DNA are necessary because the NIH funds the majority of genomic research in the US. In view of this funding, it is posited that there are sufficient incentives for scientists to continue to identify new genetic sequences through grant funding and personal/career advancement through publication. In addition to non-patent incentives for genomic research, it is also argued that granting patents to isolated DNA enables the existence of a patent thicket/anti-commons, which is more likely to hinder the development of genetic technologies, as studies have shown that scientists tend to avoid working in areas/compounds that are heavily covered by patents. *Id*. at 72.

However, the patent eligibility of subject matter should be determined under the statute in a non-discriminatory manner. The availability of private or public funding or the lack of available funding should not act as a non-statutory threshold for whether compositions are patent-eligible subject matter under the Patent Act. Likewise, the availability, or not, of non-patent incentives cannot properly distinguish a patent-eligible composition of matter under the Act from a patent-ineligible composition. Such ill-defined concepts, not rooted in section 101, should not be considered by the courts in assessing patent eligibility under section 101.

The assumptions underlying considerations of whether there are adequate incentives without patents, or whether the existence of patents creates a thicket/anti-commons, are clearly the subject of debate. This debate was noted by the *Myriad* court, which determined that the debate could not be properly resolved by the court. *Myriad* at 83. This debate is also not unique to isolated DNA. It is the same debate with other new technologies and goes to the heart of the patent system. Yet, each time this debate has reached the Supreme Court, the court has been consistent in providing an expansive definition of section 101. *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010).

There can be little debate that patents claiming isolated DNA have largely been the basis for the biotechnology industry, which provides a host of life altering innovation including therapeutic proteins, gene therapy, vaccinations, genetic testing, improved agriculture, and other future applications many of which are unforeseen today. The exclusion of isolated

DNA as patent-eligible subject matter would dramatically impact the investment into biotechnology and slow, if not disable, future innovation. The U.S. patent system is a core driver of innovation in all technologies and that system must serve without discrimination against any one technology. Accordingly, the ABA should continue to advocate for an expansive scope of section 101 applicable to all technologies, including isolated DNA compounds.

Respectfully submitted,

Marylee Jenkins, Chair
Section of Intellectual Property Law
February 2011

APPENDIX B

AMERICAN BAR ASSOCIATION

ADOPTED BY THE HOUSE OF DELEGATES

FEBRUARY 11, 2013

RESOLUTION 101A

RESOLVED, That the American Bar Association supports the principle that laws of nature, physical phenomena, and abstract ideas are not eligible for patenting as a process under 35 U.S.C. § 101, even if they had been previously unknown or unrecognized;

FURTHER RESOLVED, That the American Bar Association supports the principle that a process meets the requirements of Section 101 where—

(1) the claimed process as a whole, other than a mental process, is limited to a specific application of a law of nature, natural phenomenon, or abstract idea; or

(2) the claimed process requires or involves a transformation of matter.

FURTHER RESOLVED, That the American Bar Association supports the principle that the inquiry into subject matter eligibility for patenting under 35 U.S.C. §§ 101 is a separate and distinct requirement for patent eligibility which should be resolved independently from the conditions of patentability under Sections 102 and 103, and the requirements for obtaining a valid patent under Section 112;

FURTHER RESOLVED, That the American Bar Association opposes application of a patent eligibility test under Section 101 that imports into the patent eligibility analysis the criteria or analysis for determining patentability addressed by Sections 102 and 103, as well as the criteria required for obtaining a valid patent under Section 112.

REPORT

The Section of Intellectual Property Law requests that the House of Delegates approve this Resolution, which would support an Association *amicus curiae* brief in the U.S. Supreme Court in the case of *Association for Molecular Pathology v. Myriad Genetics*, Inc., Case No. 12-398. On September 24, 2012, the petitioners filed a petition for a writ of certiorari with the Supreme Court to review the decision of the U.S. Court of Appeals for the Federal Circuit (*Ass'n of Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303 (Fed. Cir. 2012) (*Myriad II*)). On November 30, the Supreme Court granted the petition for certiorari. This report cannot be considered by the House of Delegates at a time later than the 2013 Midyear Meeting because the deadline for filing an amicus brief on the merits in the Supreme Court will be reached before the next meeting of the House of Delegates.

Introduction and Background

The resolution deals with an issue of fundamental importance to the patent bar and the public in general, namely, the interpretation of Section 101 of the patent statute (35 U.S.C. §§ 101). Section 101 defines the types of inventions and discoveries that are eligible for patent protection. The *Myriad* case is currently under petition for a writ of certiorari by the Association for Molecular Pathology et al.

In 2010, the district court granted summary judgment for the plaintiffs, inter alia, holding one method claim from U.S. Patent No. 5,747,282 [hereinafter "Claim 20"] not patent eligible under 35 U.S.C. § 101 on grounds that certain steps claimed a basic scientific principle and other steps which were transformative were merely preparatory data gathering. *Ass'n for Molecular Pathology v. U.S. Pat. & Trademark Off.*, 702 F. Supp. 2d 181, 237 (S.D.N.Y. 2010). In 2011, the Federal Circuit reversed the district court's summary judgment, finding Claim 20 patent eligible under Section 101 because it contained a transformative step ("growing transformed cells"). *Ass'n for Molecular Pathology v. U.S. Pat. & Trademark Off.*, 653 F.3d 1329, 1357-58 (Fed. Cir. 2011) [hereinafter "*Myriad I*"]. Following its decision in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012) [hereinafter "*Mayo*"], the Supreme Court granted certiorari as requested by the Association for Molecular Pathology et al., vacated *Myriad I*, and remanded to the Federal Circuit for reconsideration under *Mayo*. 132 S. Ct. 1794 (2012). The Federal Circuit again held Claim 20 patent eligible because it comprises a step of "growing host cells transformed with an altered BRCA1 gene"—"altering a cell to include a foreign gene, resulting in a man-made, transformed cell with enhanced function and utility." *Ass'n for Molecular Pathology v. U.S. Pat. & Trademark Off.*, 689 F.3d 1303, 1336 (Fed. Cir. 2012) (emphasis in original) [hereinafter "*Myriad II*"].

The ultimate question of patentability of the invention defined by Claim 20 is not before the Court; the question before the Court relates specifically to patent eligibility of the claim. The Federal Circuit concluded that Claim 20 "applies certain steps to transformed cells that . . . are a product of man, not of nature." Myriad II, 689 F.3d at 1336. The Section of Intellectual Property recommends support of the Federal Circuit's position that respondent's claims include steps directed to transformed, man-made subject matter and are therefore patent-eligible subject matter.

The Section of Intellectual Property Law recommends that the Association support a position that a claimed process is patent eligible under Section 101 where the claimed process as a whole, other than a mental process, is limited to a specific application of a law of nature, a natural phenomenon, or an abstract idea, or alternatively where the claimed process requires or involves a transformation of matter.

The Section further recommends that the determination of subject matter eligibility for patenting under Section 101 should be resolved separately and independently from other conditions and requirements for determining patentability under Sections 102, 103, as well as criteria required for obtaining a valid patent under Section 112. Thus, the Section recommends opposing a subject matter eligibility analysis which imports the requirements of any of Sections 102, 103, or 112 into the requirements for Section 101.

Claim 20 of the Myriad patent reads as follows:

> 20. A method for screening potential cancer therapeutics which comprises:
>
> growing a transformed eukaryotic host cell containing an altered BRCA1 gene causing cancer in the presence of a compound suspected of being a cancer therapeutic,
>
> growing said transformed eukaryotic host cell in the absence of said compound,
>
> determining the rate of growth of said host cell in the presence of said compound and the rate of growth of said host cell in the absence of said compound and
>
> comparing the growth rate of said host cells, wherein a slower rate of growth of said host cell in the presence of said compound is indicative of a cancer therapeutic.

The method defined by this claim involves screening a compound to determine its potential as a cancer therapeutic by growing host cells transformed with a man-made altered breast cancer gene in the presence and absence of the compound and comparing the growth rate. The petitioner argues that Claim 20 "patents the basic scientific process of observing the naturally-occurring growth rate of a cell with a BRCA1 mutation" and does not specify any inventive steps, tools, or compound. Pet. for Cert., p. 8. Thus, according to the petitioner, Claim 20 is similar to the claims which were held patent ineligible in *Mayo*, as both Claim 20 and the claims in *Mayo* "involve[d] examining a . . . cell's natural reaction to any potential drug." Pet. for Cert., p. 31. The petitioner contends that the Federal Circuit erred when it found that Claim 20 relates to measuring how the drug affects a transformed call as opposed to the patient's body, thereby distinguishing the two types of claims and finding *Mayo* irrelevant to Claim 20's eligibility. The petitioner argues that the distinction is incorrect because Claim 20 "does not require that the cell be transformed by the patent holder." Pet. for Cert., p. 32. Comparing a compound's effect on cell growth is conventional and thus not patent eligible.

The petition for certiorari filed in this case stated the questions presented by the appeal as follows:

> Many patients seek genetic testing to see if they have mutations in their genes that are associated with a significantly increased risk of breast or ovarian cancer. Respondent Myriad Genetics obtained patents on two human genes that correlate to this risk, known as BRCA1 and BRCA2. These patents claim every naturally-occurring version of those genes, including mutations, on the theory that Myriad invented something patent eligible simply by removing ("isolating") the genes from the body. Petitioners are primarily medical professionals who regularly use routine, conventional genetic testing methods to examine genes, but are prohibited from examining the human genes that Myriad claims to own. This case therefore presents the following question:
>
> 1. Are human genes patentable?
>
> 2. Did the court of appeals err in upholding a method claim by Myriad that is irreconcilable with this Court's ruling in *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012)?

> 3. Did the court of appeals err in adopting a new and inflexible rule, contrary to normal standing rules and this Court's decision in *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118 (2007), that petitioners who have been indisputably deterred by Myriad's "active enforcement" of its patent rights nonetheless lack standing to challenge those patents absent evidence that they have been personally threatened with an infringement action?

The November 30 order of the Supreme Court granted certiorari only to Question 1. The policy proposed in the first, third, and fourth paragraphs of this resolution is particularly applicable to Question 1. Given the breadth of Question 1 and the interrelationship of composition of matter claims and process or method claims in circumstances such as those present in the *Myriad* litigation, the Supreme Court's disposition of the case may inform the patent-eligibility of such process claims generally and may also impact the patent-eligibility of Claim 20. The policy proposed in this resolution would also be applicable in any future litigation or legislative reform involving the same issues.

The petitioner's primary argument is that, if valid, Claim 20 would preempt researchers from using this technology to find cancer treatments, and therefore is contrary to Supreme Court precedent.

The Federal Circuit interpreted Claim 20 to comprise a transformative step—growing transformed cells. The Section of Intellectual Property Law believes that the claims define patent eligible subject matter. Contrary to petitioner's argument, the method defined by claim 20, as construed by the Federal

Circuit, when considered as a whole, is not a law of nature, a natural phenomenon, or an abstract idea—subject matter which the Supreme Court has held are the only limitations on the scope of patent eligible subject matter under Section 101. *Bilski*, 130 S. Ct. at 3225. Instead, Claim 20 requires a transformative step, which does not fall within any of the three categories mentioned above as the only limitations on the scope of patent eligible subject matter under Section 101. The Section recommends that the Association take no position on whether Claim 20 complies with the other patentability criteria under the statute, namely Sections 102, 103, and 112. Patent eligibility for such methods is important to incentivize investment into the research and development.

The Court of Appeals Decisions

In its July 2011 decision, the Federal Circuit reversed the district court's summary judgment that Claim 20 was not patent eligible under Section 101. *Myriad I*, 653 F.3d at 1357-58. To determine patent eligibility, the Myriad court began with the machine-or-transformation test set forth in its decision in *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008) (en banc), *aff'd*, *Bilski v. Kappos*, 130 S. Ct. 3218 (2010). Under that test, "A claimed process is surely patent-eligible under § 101 if: (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing." *Id.* at 954. The Supreme Court later clarified that the machine-or-transformation test is not the sole test for patent eligibility, but may be an important and useful clue. *Bilski*, 130 S. Ct. at 3221.

According to *Myriad I*, the first step of Claim 20 was a transformative growing of cells, a step which caused a physical manipulation of the cells. The second step, determining the growth rate of the cells, was also transformative because it, too, required physical manipulation of the cells. In that step, "determining" referred to an assay or physical test which measured the quantity of cells. Furthermore, the transformative steps were not extra-solution activities or merely data gathering steps, but instead, those steps were found to be central to the goal of the process. The court also reviewed whether the claims fell into the prohibited categories, determining that the claim was not "so 'manifestly abstract' as to claim only a scientific principle, and not a patent-eligible process." *Prometheus*, 628 F.3d at 1358 (citing *Research Corp. Techs., Inc. v. Microsoft Corp.*, 627 F.3d 859, 869 (Fed. Cir. 2010). Thus, the court held that Claim 20 claimed patentable subject matter under Section 101.

Following the decision in *Myriad I*, the Association for Molecular Pathology et al. filed a petition for certiorari with the Supreme Court.

In March 2012, while the *Myriad I* petition for certiorari was pending, the Supreme Court issued its decision in *Mayo*. In that decision, the Supreme Court reiterated its earlier statement in *In re Bilski* that the Federal Circuit's "machine or transformation" test, while providing a valuable clue in determining whether a patent claim is directed to patent-eligible subject matter, is not the sole test for Section 101 compliance. *Mayo*, 132 S. Ct. 1289, 1296 (citing *In re Bilski*, 130 S. Ct. 3218, 3221 (2010)).

The claims in *Mayo* dealt with a process for optimizing the therapeutic efficacy of a method for treating an immune-mediated gastrointestinal disorder, such as Crohn's disease. A representative claim of the Prometheus patent reads as follows:

> A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
>
> (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,
>
> wherein the level of 6-thioguanine less than about 230 pmol per 8 x 10^8 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and
>
> wherein the level of 6-thioguanine greater than about 400 pmol per 8 x 10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

In general, the method defined by this claim involved the administration of a pro-drug, such as a 6-mercaptopurine, to a patient suffering from immune-mediated gastrointestinal disorders. According to the patent, the pro-drug is metabolized in the human body to certain metabolites, such as 6-thioguanine. The patent indicated that patients treated with these types of drugs sometimes experienced toxic side effects if the dosage were too high or lack of efficacy if the dosage were too low. To solve that problem, the patent described a process that involved administering the pro-drug, determining the level of the metabolite in the bloodstream and comparing the metabolite blood levels to certain established minimum and maximum values, such that the dosage could be optimized to ensure therapeutic efficacy with minimal side effects.

Similar to *Myriad I*, the Federal Circuit had held that the *Mayo* claims required transformative steps—administering and determining. The Supreme Court disagreed. Finding the claims patent ineligible, the Court explained:

> First, the "administering" step simply refers to the relevant audience, namely doctors who treat patients with certain diseases with thiopurine drugs. That audience is a pre-existing audience; doctors used thiopurine drugs to treat patients suffering from autoimmune disorders long before anyone asserted these claims. In any event, the "prohibition against patenting abstract ideas 'cannot be circumvented by attempting to limit the use of the formula to a particular technological environment.'" *Bilski*, supra, at ___, 130 S. Ct. 3218, 3225 [2010] (quoting *Diehr*, 450 U.S., at 191-92, 101 S. Ct. 1048).
>
> Second, the "wherein" clauses simply tell a doctor about the relevant natural laws, at most adding a suggestion that he should take those laws into account when treating his patient. That is to say, these clauses tell the relevant audience about the laws while trusting them to use those laws appropriately where they are relevant to their decision making (rather like Einstein telling linear accelerator operators

about his basic law and then trusting them to use it where relevant).

Third, the "determining" step tells the doctor to determine the level of the relevant metabolites in the blood, through whatever process the doctor or the laboratory wishes to use. As the patents state, methods for determining metabolite levels were well known in the art. '623 patent, col. 9, ll. 12-65, 2 App. 11. Indeed, scientists routinely measured metabolites as part of their investigations into the relationships between metabolite levels and efficacy and toxicity of thiopurine compounds. '623 patent, col. 8, ll. 37-40, id., at 10. Thus, this step tells doctors to engage in well understood, routine, conventional activity previously engaged in by scientists who work in the field. Purely "conventional or obvious" "[pre]solution activity" is normally not sufficient to transform an unpatentable law of nature into a patent eligible application of such a law. *Flook*, 437 U.S., at 590, 98 S. Ct. 2522; *see also Bilski*, 561 U. S., at ___, 130 S. Ct. 3218, 3225 ("[T]he prohibition against patenting abstract ideas 'cannot be circumvented by' . . . adding 'insignificant postsolution activity'" (quoting *Diehr*, *supra*, at 191-192, 101 S. Ct. 1048)).

* * *

[T]he claims inform a relevant audience about certain laws of nature; any additional steps consist of well understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant be-

> yond the sum of their parts taken separately. For these reasons we believe that the steps are not sufficient to transform unpatentable natural correlations into patentable applications of those regularities.

Mayo, 132 S. Ct. at 1297-98 (parallel citations omitted).

Following its decision in Mayo, the Supreme Court granted certiorari in *Myriad I*, and summarily vacated and remanded the decision, with instructions that the Federal Circuit reconsider its decision in light of the Supreme Court's decision in Mayo. On August 16, 2012, the Federal Circuit issued its decision in *Myriad II*, again finding Claim 20 to be drawn to patent eligible subject matter.

The Federal Circuit again found Claim 20 patent eligible under Section 101 because it comprises a step of "growing host cells transformed with an altered BRCA1 gene"—"altering a cell to include a foreign gene, resulting in a man-made, transformed cell with enhanced function and utility." *Myriad II*, 689 F.3d at 1336. Comparing Claim 20 to *Mayo*, the Federal Circuit stated:

> The Court, in its evaluation of the *Mayo* method claims, found that the additional steps of those claims were not sufficient to "transform" the nature of the claims from mere expression of natural laws to patent-eligible subject matter. By definition, however, performing operations, even known types of steps, on, or to create, novel, *i.e.*, transformed subject matter is the stuff of which most process or method invention consists. All chemical processes, for

> example, consist of hydrolyzing, hydrogenating, reacting, etc. In situations where the objects or results of such steps are novel and nonobvious, they should be patent-eligible. It is rare that a new reaction or method is invented; much process activity is to make new compounds or products using established processes. Thus, once one has determined that a claimed composition of matter is patent-eligible subject matter, applying various known types of procedures to it is not merely applying conventional steps to a law of nature. The transformed, man-made nature of the underlying subject matter in claim 20 makes the claim patent-eligible. The fact that the claim also includes the steps of determining the cells' growth rates and comparing growth rates does not change the fact that the claim is based on a man-made, non-naturally occurring transformed cell—patent-eligible subject matter.

Id. at 1336 (emphasis added).

Additionally, the Federal Circuit held that Claim 20 does not preempt all methods for determining the therapeutic effect of a potential compound. Instead, it is specifically related to certain host cells transformed with a certain gene. Thus, the court found Claim 20 to be patent eligible subject matter under Section 101. *Id.* at 1337.

Inventions Should Not Be Denied Patent Eligibility Under Section 101 Where the Claimed Process Is Limited to a Specific Application of a Law of Nature, Natural Phenomenon, or Abstract Idea, or Where the Claimed Process Requires or Involves a Transformation of Matter.

As the Supreme Court held in *Bilski*, a broad reading of Section 101 is mandated by both the expansive text of the statute and Supreme Court precedent. The Supreme Court's precedents provide three specific exceptions to the broad patent-eligibility principles of Section 101: laws of nature, natural phenomena, and abstract ideas. The Supreme Court has held that "these exceptions have defined the reach of the statute as a matter of statutory stare decisis going back 150 years." *Bilski*, 130 S. Ct. at 3225 (citation omitted).

A broad reading of Section 101 is also supported by the fact that "[t]he § 101 patent-eligibility inquiry is only a threshold test." *Bilski*, 130 S. Ct. at 3225; see also 35 U.S.C. § 101 (a claim drawn to patent eligible subject matter is entitled to a patent only "subject to the conditions and requirements of this title"). Thus, Section 101 is a coarse filter, with more rigorous patentability analysis required by 35 U.S.C. §§ 102 (novelty) and 103 (non-obviousness), and conditions for a valid patent under § 112 (adequate written description and enablement support, best mode disclosure and definiteness of claim language).

The petitioner challenges the claim at issue here by arguing that Claim 20, like the claims held by the Supreme Court to be patent ineligible subject matter in *Mayo*, involves examining the natural reaction of a patient's cell to a potential drug, broadly preempting the use of the process to screen any potential cancer therapeutic. The Federal Circuit rejected this argument and held that Claim 20 applies certain process steps to transformed cells—cells which are man-made, not natural—and does not preempt all use of the process. The inclusion of a transformation of matter removes the claim from the three categories of excluded subject matter, passing the coarse filter requirement for patent eligible subject matter under Section 101. Thus, as long as the patent does not claim or preempt purely natural phenomena, methods or processes for screening potential therapeutics should be patent eligible under Section 101.

The claim at issue, when considered as a whole, does not cover prohibited laws of nature, natural phenomena, or abstract ideas. The first two steps of the claim require growing of host cells transformed with a specific altered gene in the presence or absence of a potentially therapeutic compound. This transformative "growing" step does not occur in nature because the cell which is grown does not occur in nature; an altered cell is required by the claim It requires a man-made object upon which to act. This step necessarily falls outside of the three exclusions for patent eligible subject matter laid out by Supreme Court precedent, thereby meeting the requirement for patent eligibility under Section 101. Whether the claim is overly broad under the statute (and therefore invalid) is a patentability issue under Sections 102, 103 and 112, and not a patent eligibility issue under Section 101.

The Analysis of Patent Eligible Subject Matter Under Section 101 Should Be a Separate and Distinct Analysis from a Patentability Analysis Under 35 U.S.C. §§ 102 or 103 or the Analysis of Conditions for Obtaining a Valid Patent Under Section 112.

In *Mayo*, the Supreme Court provided additional commentary relating to "further arguments in support of Prometheus' position" which did not contribute to the holding of the case. 132 S. Ct. at 1302-05. However, this commentary and its relation to the patent eligibility analysis in the case has led to much discourse among patent practitioners regarding the conflation of Section 101 with other sections of the patent law, particularly Sections 102, 103, and 112. In view of this, the process for analysis of patent eligible subject matter under Section 101 needs to be clarified.

Title 35 provides separate and distinct sections for determining the types of inventions which are (a) patent eligible (§ 101); (b) novel—a condition for patentability (§ 102); (c) non-obvious subject matter—another condition for patentability (§ 103); and (d) required conditions for obtaining a valid patent (§ 112). Each of these requirements is laid out separately and distinctly in the patent law. No section cross-references another section by stating that conditions for the cross-referenced section must also be met in order to meet the conditions of that particular section. Instead, the requirements are described as individual, non-dependent requirements, all of which must be met to obtain a valid patent.

The distinction between these requirements has been noted in court precedent as well.

> The § 101 patent-eligibility inquiry is only a threshold test. Even if an invention qualifies as a process, machine, manufacture, or composition of matter, in order to receive the Patent Act's protection the claimed invention must also satisfy "the conditions and requirements of this title." § 101. Those requirements include that the invention be novel, see § 102, nonobvi-

> ous, see § 103, and fully and particularly described, see § 112.

Bilski, 130 S. Ct. at 3225. This "threshold test" argument was submitted by the U.S. Government as amicus curiae in Mayo, saying that "virtually any step beyond a statement of a law of nature itself should transform an unpatentable law of nature into a potentially patentable application sufficient to satisfy § 101's demands." *Mayo*, 132 S. Ct. at 1303. Once the minimum requirements for patent eligibility have been met, the other conditions for obtaining a valid patent required by Sections 102, 103 and 112 may be adequately used to determine patentability and validity.

The *Mayo* court responded to the Government's threshold test argument, saying:

> We recognize that, in evaluating the significance of additional steps, the § 101 patent eligibility inquiry and, say, the § 102 novelty inquiry might sometimes overlap. But that need not always be so. And to shift the patent eligibility inquiry entirely to these later sections risks creating significantly greater legal uncertainty, while assuming that those sections can do work that they are not equipped to do.

Id. at 1304. This dicta in *Mayo* has disrupted the settled precedent, which states:

> It has been urged that novelty is an appropriate consideration under § 101. Presumably, this argument results from the language in § 101 referring to any "new and useful" process, machine, etc. Section 101, however, is a general statement of the type of subject matter

that is eligible for patent protection "subject to the conditions and requirements of this title." Specific conditions for patentability follow and § 102 covers in detail the conditions relating to novelty. The question therefore of whether a particular invention is novel is "wholly apart from whether the invention falls into a category of statutory subject matter." *In re Bergy*, 596 F.2d 952, 961 (C.C.P.A. 1979) (emphasis deleted). *See also Nickola v. Peterson*, 580 F.2d 898 (6th Cir. 1978). The legislative history of the 1952 Patent Act is in accord with this reasoning. The Senate Report stated:

> Section 101 sets forth the subject matter that can be patented, 'subject to the conditions and requirements of this title.' The conditions under which a patent may be obtained follow, and Section 102 covers the conditions relating to novelty."

S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952) (emphasis supplied).

It is later stated in the same Report: "Section 102, in general, may be said to describe the statutory novelty required for patentability, and includes, in effect, an amplification and definition of 'new' in section 101." Id. at 6.

Finally, it is stated in the "Revision Notes": "The corresponding section of [the] existing statute is split into two sections, section 101 relating to the subject matter for which patents may be obtained, and section 102 defining statutory novelty and stating other conditions for patentability." *Id.* at 17.

> In this case, it may later be determined that the respondents' process is not deserving of patent protection because it fails to satisfy the statutory conditions of novelty under § 102 or nonobviousness under § 103. A rejection on either of these grounds does not affect the determination that respondents' claims recited subject matter which was eligible for patent protection under § 101.

Diamond v. Diehr, 450 U.S. 175, 190-91 (1981). Based on Supreme Court precedent and legislative history, clearly, the different sections of Title 35 are separate and distinct requirements. Contrary to the dicta in Mayo, the analysis of patent eligibility for subject matter of a claimed invention under Section 101 should not overlap with the analyses of patentability under Sections 102 and 103 or the requirements for obtaining a valid patent under Section 112. To conflate any one of these requirements with another would violate the principle of stare decisis and frustrate the legislative intent of the Patent Act.

Because Sections 101, 102, 103, and 112 are separate and distinct inquiries which should be resolved independently from one another, the Section of Intellectual Property recommends opposing any formulation of a patent eligibility test under Section 101 that imports into the patent eligibility analysis the criteria or analysis for determining patentability addressed by Sections 102 and 103, as well as the criteria required for obtaining a valid patent under Section 112.

Conclusion

A process such as that in Claim 20 does not fall within the noted exclusions from patent eligible subject matter. Contrary to the petitioner's arguments, Claim 20 involves more than a law of nature, natural phenomenon, or abstract idea; it requires a transformative step on a man-made host cell which has been transformed to include a specific altered gene. Nor does it preempt all use of a law of, natural phenomenon, or abstract idea. This process is used to screen potential drugs by growing man-made cells. A basic purpose of the patent system is to provide an economic incentive to inventors and investors to discover and develop new methods and products for the overall benefit of society. Denying patent eligibility to methods that involve a transformative step simply because the methods involve genes and cells—even man-made genes and cells—would remove this incentive.

Respectfully submitted,

Joseph M. Potenza, Chair
Section of Intellectual Property Law
February 2013

AMICUS
CURIAE
BRIEF

RECORD
AND
BRIEFS

Supreme Court, U.S.
FILED
JAN 31 2013
OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,
Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF FOR THE AMERICAN INTELLECTUAL PROPERTY LAW ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF AFFIRMANCE BUT IN SUPPORT OF NEITHER PARTY

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January 31, 2013

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INTEREST OF *AMICUS CURIAE*

The American Intellectual Property Law Association ("AIPLA") submits this brief as amicus curiae in support of affirmance (but in support of neither party on the ultimate merits of the case), in order to present its views on the correct rule of law that applies to patent eligibility.[1] AIPLA is a national bar association of approximately 14,000 members engaged in private and corporate practice, in government service, and in the academic community. AIPLA represents a wide and diverse spectrum of individuals, companies, and institutions involved directly and indirectly in the practice of patent, trademark, copyright, and unfair competition law, as well as other fields of law affecting intellectual property. AIPLA members represent both owners and users of intellectual property, thus representing the interests of both plaintiffs and defendants in IP litigation. AIPLA has no stake in any of the parties to this litigation or in the result of this case other than its interest in the issue of patent-eligible subject matter, which is vital to most, if not all, of AIPLA's members.[2]

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[1] In accordance with Supreme Court Rule 37.6, amicus curiae states that this brief was not authored, in whole or in part, by counsel to a party, and that no monetary contribution to the preparation or submission of this brief was made by any person or entity other than the amicus curiae or its counsel. After reasonable investigation, AIPLA believes that (i) no member of its Board or Amicus Committee who voted to file this brief, or any attorney in the law firm or corporation of such a member, represents a party to this litigation, (ii) no representative of any party to this litigation participated in the authorship of this brief, and (iii) no one other than AIPLA, or its members who authored this brief and their law firms or employers, made a monetary contribution to the preparation or submission of this brief.

SUMMARY OF ARGUMENT

The question presented is: "Are human genes patentable?" This question, however, does not capture the issues in this appeal.

Myriad's patents do not claim "human genes" as they exist in the body. Rather, the claims cover "isolated" DNA molecules—man-made, discrete chemical entities that differ markedly from genes as they exist in the human body. Those inventions, not any human genes, are the proper focus of the section 101 analysis required in this appeal. Genes in their native form, as part of human chromosomes, build and maintain cells. Myriad's isolated DNA molecules do not and cannot perform the functions of native genes. Rather, they can serve as functional biological tools that allow health care practitioners to identify individuals at significant risk of breast and ovarian cancer, to tailor existing treatment options for highest likelihood of therapeutic success, and to develop new anti-cancer treatments specifically designed to combat these devastating diseases.

These differences distinguish the claimed isolated DNA molecules from patent-ineligible

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[2] In accordance with Supreme Court Rule 37.3(a), the parties have consented to the filing of this amicus brief in support of neither party. The consents are submitted herewith.

"products of nature" under this Court's prior decisions in *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948), and *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1 (1931). Each of those cases focused the patent eligibility inquiry on whether the claimed subject matter had markedly different characteristics compared to nature's handiwork, as well as on the subject matter's potential for significant utility. Applying those standards, the Federal Circuit correctly held that the claimed isolated DNA molecules passed muster under section 101. *See* Pet. App. 2a-119a.

To be sure, "human genes" as they exist in the body are not "patent eligible" under 35 U.S.C. § 101; they also are not patentable under other provisions of patent law. For instance, human genes are not "new" and therefore a claim to a human gene would be anticipated by naturally occurring human genes in contravention of 35 U.S.C. § 102. "Patentability," however is not at issue in this case. "Patentability" refers to compliance with all statutory provisions that govern whether a patent is valid and enforceable, including those directed to, *inter alia*, obviousness, anticipation, enablement, and written description. The focus of this appeal is solely on 35 U.S.C. § 101, the gatekeeper provision that determines what subject matter is ***eligible*** for patent protection.

This Court's recent ruling in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* does not require reversal of the Federal Circuit's decision. In *Prometheus*, a law of nature—namely, the relationship between certain levels of a drug metabolite and its safety and efficacy—was deemed central to the method claim at issue. 566 U.S. __, 132 S.Ct. 1289, 1294 (2012). This Court therefore looked to its precedents involving methods that implicate laws of nature and abstract ideas, including *Parker v. Flook*, 437 U.S. 584 (1978), and *Diamond v. Diehr*, 450 U.S. 175 (1981). Applying a test discerned from those cases, the Court examined Prometheus's method claims to determine whether they "do significantly more than simply describe [the] natural relations" at the heart of those claims. *Prometheus*, 132 S.Ct. at 1297.

Prometheus did not overrule any of the cases, including *Chakrabarty*, that the Federal Circuit relied upon to find that Myriad's isolated DNA products fall within the scope of section 101. Nor did *Prometheus* introduce a new test for patent eligibility that would conflate section 101 with sections 102, 103, and/or 112—they are separate. The test set forth in *Chakrabarty* and applied by the Federal Circuit properly governs the section 101 inquiry with respect to Myriad's claims to isolated DNA molecules. *See* Pet. App. 48a-52a.

Among the misleading charges made by those who would exclude this subject matter for patent protection is the contention that scientists and researchers would be barred from examining and experimenting with the claimed material. This contention, however, fails to recognize the long-standing experimental use exception that immunizes non-commercial research with patented material; it also fails to recognize the statutory provision permitting uses of patent inventions for conducting clinical testing necessary for obtaining FDA approval. 35 U.S.C. § 271(e)(1).

In sum, discrete, man-made chemical entities that serve as important medical tools are exactly the type of invention that the patent laws and their underlying policies are designed to incentivize and protect. Those policies are, as they should be, blind to the raw materials from which significant technological advances spring. Indeed, the USPTO, the courts, and Congress have recognized that inventions derived from naturally occurring substances but imbued with different characteristics and uses constitute protectable "compositions of matter" or "manufactures" under section 101. To reverse course and now deem the claimed isolated DNA molecules ineligible for patent protection without an express directive from Congress would disrupt not only well settled law but also the expectations of patent owners and inventors.

ARGUMENT

I. MYRIAD'S CLAIMED DNA MOLECULES ARE NOT PRODUCTS OF NATURE

An analysis under section 101 must start with an understanding of what is—and what is not—claimed. *See In re Bilski*, 545 F.3d 943, 951 (Fed. Cir. 2008), *aff'd*, 130 S. Ct. 3218 (2010)("[c]laim construction ... is an important first step in a § 101 analysis"). By way of example, claim 1 of U.S. Patent No. 5,747,282 ("the '282 Patent") states:

> 1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.

2J.A. 822, '282 Patent at col. 153, ll. 55-58. SEQ ID NO:2 sets forth the amino acid sequence of the BRCA1 protein. Pet. App. 10a-11a. Claim 1 does not recite the phrase "human gene." Nor does it cover "human genes," which are integral portions of the intact, native human genome. It does, however, recite "DNA," albeit in "isolated" form.

A. Human DNA Is Complex in Both Structure and Function

DNA refers to a large class of compounds all sharing a common chemical backbone.[3] Pet. App. 14a. Each DNA molecule has chemical components called nucleotides, or nucleotide bases, which are referred to for ease of reference as A, T, C, and G. Pet. App. 14a. The term "DNA," as it refers broadly to a chemical class, encompasses both native, genomic DNAs (as found in the body) as well as DNAs that are wholly designed and synthesized by man. Pet. App. 18a-20a.

In the human body, the entire genome consists of twenty-three pairs of chromosomes, each of which is a complex structure comprising a single DNA molecule wrapped around proteins called histones. Pet. App. 18a-19a. Native chromosomes have at least 80 million nucleotides. Pet. App. 51a. The order of the nucleotide bases in a DNA molecule is called the "sequence," but what the "sequence" actually represents is the precise configuration of the component chemical nucleotides that make up a single, large chemical compound.

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[3] The Federal Circuit has provided an excellent summary of the technology involved in this case. We address certain pertinent points here.

Each native DNA molecule consists of a long chemical chain of millions of nucleotide base pairs, and different portions of the DNA have different functions. Certain regions of the DNA chain are known as "genes" and hold the genetic code for the various proteins required to sustain life. Pet. App. 257a-259a. The human genome comprises a vast number of such genes along with other sequences, or portions of the DNA molecule interspersed. *See* Pet. App. 18a-19a; Pet. App. 259a ("25,000 genes in the human body make up the human genome."). A human gene, from a structural perspective, is simply one portion of a vastly complex, highly regulated chemical entity.

Most human genes contain both exons (the sequences that actually code for the protein) and introns (areas believed to contain non-coding sequences). Pet. App. 15a. The BRCA1 and BRCA2 genes are no exception. As they exist in the human body, each consists of tens of thousands of nucleotides, the vast majority of those being intron sequences. Pet. App. 51a-52a. Certain of the claimed isolated DNA molecules in Myriad's patent, however, contain just the coding exons, and no non-coding introns.

Not only are genes structurally complex, but they are functionally complex as well, instructing the human body on its growth and development. The BRCA1 and BRCA2 genes and the proteins they encode are part of the mechanism by which the genome repairs itself and are referred to as caretaker genes. But these two BCRA genes don't play that role by themselves. They are part of an intricate, highly regulated system that involves a variety of cellular components to both activate and effectuate the repair of the genome when it has been damaged.

B. Myriad Claims Isolated DNA Molecules, Not Found in Humans, That Can Perform New Functions

A comparison between those human genome portions designated as BRCA1 and BRCA2 to what is actually claimed in Myriad's patent must begin with the claim language. Claim 1 of the '282 patent is a representative example.

The claim uses the term "isolated" to introduce its description of the DNA, which immediately indicates that the claim is directed to something other than human genes as found in the human body. *See* 2J.A. 755, '282 Patent at col. 19, ll. 8-19 (indicating "isolated" includes DNA that "has been removed from its naturally occurring environment"). Despite the impression that the term "isolated" may create for a lay person, it is not the case that one can hold down a DNA molecule and, using a scalpel, simply cleave off the portion that corresponds to the BRCA1 or BRCA2 gene.

Instead, to obtain an isolated DNA molecule, scientists extract chromosomal DNA from cells and then, using scientific methods, obtain shorter and shorter fragments. Pet. App. 2a, 51a-52a. These fragments have a variety of random lengths and composition, and they must be arranged and ultimately put in sequence order. Contrary to what some might imply, when the DNA is cut, it does not cleanly and neatly separate into individual genes, nor does the process simply cast aside the non-coding regions. Pet. App. 51a-54a.

This process results in the creation of a new chemical entity that did not exist before. Pet. App. 51a-54a. True, the new chemical has some nucleotides in the same order as found in DNA as it exists in the body. But the fact that a wholly new chemical is derived from, and even shares the same chemical units with, a chemical that exists in nature has never been the basis for excluding a claimed chemical compound from the scope of patentability in section 101. *See* Pet. App. 87a (Moore, J., concurring-in-part)(citing *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95 (S.D.N.Y. 1911), and comparing Myriad's isolated DNA molecules to adrenaline).

Claim 1 of the '282 patent, having required isolation, then continues: "DNA coding for a BRCA1 polypeptide." This describes a subclass of DNA molecules: those that have the precise chemical composition (*i.e.*, nucleotide sequence) corresponding to the amino acids that make up the BRCA1 protein. Those isolated molecules cannot function like the native DNA from which they are derived. They are not part of a highly regulated genome that instructs the growth and development of humans. They cannot participate in the body's genomic repair mechanism, let alone regulate in the same fashion.

Instead, the newly created DNA molecules as claimed perform new functions that native DNA cannot perform. They can be used as biological tools to diagnose illness and are instrumental in tailoring treatment options to ensure therapeutic success. They can be used to develop new, carefully targeted anti-cancer treatments to benefit mankind. These are significant new utilities that flow directly from inventors' creation of a new composition of matter.

II. THE FEDERAL CIRCUIT APPLIED THE CORRECT TEST

A. Patent Eligibility of Isolated DNA Molecules, Which Are Compositions of Matter, Must Be Analyzed Under the Applicable Precedents

The Federal Circuit correctly recognized that this Court's decisions in *Chakrabarty* and *Funk Brothers* "set out the primary framework for deciding the patent eligibility of compositions of matter, including isolated DNA molecules." Pet. App. 48a. The issue in *Chakrabarty* was whether a living organism—a bacterium created by scientists—was eligible for patent protection under the "product of nature" exception to section 101. *See* Pet. App. 49a (citing *Chakrabarty*, 447 U.S. at 305, 307). Through genetic engineering, the inventors created a bacterium that did not exist in nature in the claimed form. It had four naturally occurring DNA molecules from different sources, each enabling the breakdown of a different component of crude oil. The new bacterium (with its four oil-eating DNA molecules) was more efficient in treating oil spills than any naturally occurring bacteria. Pet. App. 49a. This Court concluded that the man-made bacterium qualified as patent-eligible subject matter because it was a "product of human ingenuity" having "markedly different characteristics from any found in nature and one having the potential for significant utility." *Chakrabarty*, 447 U.S. at 309-10.

Funk Brothers and other Supreme Court decisions have likewise focused on the distinction between "products of nature, whether living or not, and *human-made* inventions." *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 130 (2001)(quoting *Chakrabarty*, 447 U.S. at 313)(emphasis added). In *Funk Brothers*, the patentee discovered a harmonious relationship between certain strains of naturally occurring bacteria. 333 U.S. at 131. When grouped together in a mixed culture, the combination had improved plant-protective properties as compared to any single bacterium. This Court, however, held that the bacteria's cooperative quality was the "work of nature" and thus not patentable. *Id.* at 130. Unlike the case in *Chakrabarty*, where the inventors created something entirely new and different from anything found in nature, the discovery in *Funk Brothers* resulted from merely observing a natural phenomenon, not from any functional or structural improvement by human intervention.

Applying that framework to the present case, the Federal Circuit correctly held that Myriad's isolated DNA is not nature's handiwork, but that of Myriad's scientists who used skill and ingenuity to produce compositions of matter not found in the body. *See* Pet. App. 48a, 50a-51a. The Federal Circuit thus properly applied the *Chakrabarty* inquiry to determine whether Myriad's claimed compositions have "markedly different" or "distinctive" characteristics when compared to compositions found in nature. Pet. App. 48a-54a.

In so holding, the Federal Circuit took particular note of the substantial differences in size and structure between the native genome and Myriad's claimed isolated DNA molecules. Pet. App. 51a. For example, in contrast to human chromosomes having at least 80 million nucleotides, each of the isolated BRCA1 and BRCA2 DNA molecules consists of about 80,000 nucleotides. But when non-coding introns are removed, the isolated DNA molecules shrink to 5,500 and 10,200 nucleotides respectively. Pet. App. 51a. Some of the claims at issue cover isolated DNA molecules having as few as fifteen nucleotides. Accordingly, the claimed isolated DNA molecules have chemical identities that are different from "human genes." And those differences were wrought by human intervention to both isolate discrete structures and produce utility. Pet. App. 51a-53a.

In sum, the Federal Circuit correctly recognized that Myriad's discovery of isolated DNA entails far more than identifying and observing a natural phenomenon as in *Funk Brothers*. Rather, Myriad's invention involved significant human effort to markedly transform DNA and then find new characteristics and uses for the isolated fragments. It thus meets the standards for patent eligibility established by this Court in *Chakrabarty*.

B. *Prometheus* Applies to Method Claims, Not to the Isolated DNA Molecule Claims at Issue Here

This Court's *Prometheus* decision reaffirmed that, while inventions covered by laws of nature, natural phenomena, and abstract ideas may not be patented on their own, a process that "applies" a fundamental principle in one of these categories may be patentable if it does "significantly more" than just recite a law of nature with instructions to "apply it." *Prometheus*, 132 S. Ct. at 1293-94.

Much of the *Prometheus* decision explored the "significantly more" quality that transforms an unpatentable principle into a patentable "application" of that principle. *Id.* This requirement of "significantly more" harmonizes the various approaches taken by the Supreme Court over the years. *See, e.g., Gottschalk v. Benson*, 409 U.S. 63, 71-72 (1972)(rejecting claims that "would wholly pre-empt the mathematical formula and in practical effect would be a patent on the algorithm itself"); *Prometheus*, 132 S. Ct. at 1294.[4]

However, Myriad's method claims are not at issue here, so the criteria for patent eligibility set forth in *Prometheus*, which apply to method claims that implicate laws of nature, do not apply to composition claims such as Myriad's claims to isolated DNA molecules. *Prometheus* did not overrule *Chakrabarty* or its predecessors. Nor did it opine on the applicability of the rationale of such precedents to isolated biological materials.

C. Myriad's Claims May Not Be Patentable, But That Does Not Make Them Patent-Ineligible Under Section 101

As written, Myriad's isolated DNA claims potentially cover an enormous number of molecules. For at least this reason, patent practitioners can and do differ on the question of whether the claims at issue in this case on this record satisfy certain provisions of the patent laws pertaining to patentability, including those governing, for example, obviousness, enablement and written description.[5] *See, e.g.*, *Diehr*, 450 U.S. at 188-89. But, whether those claims ultimately are valid and enforceable raises a question that is far different from whether they recite patent-eligible subject matter under section 101.

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[4] Consistent with Supreme Court precedent as applied in *Prometheus*, the Federal Circuit properly concluded that one of Myriad's claimed screening methods (claim 20) included transformative steps that include "more than [an] abstract mental step" and do "not simply apply a law of nature" because the claimed method involved growing transformed cells and physically manipulating the cells to determine growth rates. Pet. App. 68a-69a.

This Court in *Prometheus* did not announce a wholesale conflation of section 101 with sections 102 (novelty) and 103 (non-obviousness). Rather, applying *Bilski*, *Flook*, *Benson*, and *Diehr*, the Court explained that it had resisted any "temptation to depart from case law precedent." *Prometheus*, 132 S. Ct. at 1298-02. As *Diehr*, for instance, makes clear, "[t]he 'novelty' of any element or steps in a process, or even of the process itself, is of no relevance in determining whether the subject matter of a claim falls within the § 101 categories of possibly patentable subject matter." *Diehr*, 450 U.S. at 188-89. Indeed, whether one or more steps in a process is "novel or independently eligible for patent protection is irrelevant to the question of whether the claims as a whole recite subject matter *eligible* for patent protection under § 101." *Id.* at 193, n.15.

Consistent with precedent, novelty and non-obviousness are and should remain separate, independent requirements, each with its own distinct elements, proofs, and precedents. Both of those requirements for patentability can entail complex legal, technical, and factual inquiries regarding the state of the art, the contents of the relevant scientific literature, the inventor's work, and the invention's development and success. And over many decades and hundreds of decisions, the courts have developed a rich body of decisions to guide both of those separate patentability inquiries. Thus, an analysis that imports the requirements of novelty and non-obviousness into section 101 would risk turning determinations of patent eligibility into unmanageable exercises, dislodged from long-established and well-understood principles.

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[5] AIPLA takes no position on the patentability of the claims at issue here.

It may be appropriate to consider how Myriad produced the claimed subject matter in order to determine whether it is man-made and to better understand the extent to which it differs from products of nature. However, it is not germane to ask whether those methods should be deemed "routine," "conventional," or "well-understood," if those terms are synonyms for lack of novelty under section 102 or obviousness under section 103.

III. PATENT PREEMPTION DOES NOT PRECLUDE THE PATENTABILITY OF THE CLAIMED SUBJECT MATTER

Laws and phenomena of nature are not entitled to patent protection as they are "free to all men and reserved exclusively to none." *Funk Bros.*, 333 U.S. at 130. Another expression of the same exclusionary principle is that patent claims may not "preempt the use of a natural law." *Prometheus*, 132 S. Ct. at 1294.

However, a concern for that kind of "preemption" should not be allowed to undermine the legitimate "preemption" that is an essential feature of any patent system—an award of exclusive rights for a limited time granted to one who creates a new and nonobvious invention. This Court has recognized that "too broad an interpretation of this exclusionary principle could eviscerate patent law." *Id.* at 1293.

A. The Importance of Broad Patent Eligibility

Congress envisioned Section 101 as broad, flexible, and adaptable to new technologies and advances in knowledge. *See Bilski*, 130 S. Ct. at 3225 (citing *Chakrabarty*, 447 U.S. at 308). "Congress took this permissive approach to patent eligibility to ensure that 'ingenuity should receive a liberal encouragement.'" *Bilski*, 130 S. Ct. at 3225 (citing *Chakrabarty*, 447 U.S. at 308-09 (quoting 5 The Writings of Thomas Jefferson 75-76 (H. Washington ed., 1871))). In keeping with that legislative directive, each advance in technology—from the Industrial Age through the Information Age and beyond—has been spurred on and rewarded by robust patent protection. And in every age, the ultimate beneficiary of patent exclusivity has been the public.

Few would dispute that a company that discovers, tests, and brings to market a novel lifesaving therapy, while risking hundreds of millions of dollars, should be free from competition for a limited period, and thus be able to recoup its enormous investment costs, fund additional research, and expand its business.[6] That patents provide such market exclusivity has never been a basis for denying or curtailing patent protection for worthy inventions. It is, in fact, the bargain established in the Constitution in order to "promote the Progress of ... useful Arts, by securing for limited Times to ... Inventors the exclusive Right to their ... Discoveries." U.S. CONST. ART I, § 8 ¶ 8.

Significantly, patents spur even more innovation. The fundamental *quid pro quo* of the patent grant is the requirement that inventors fully disclose their inventions so their knowledge, insights, and achievements become available to everyone, especially to competing innovators, who can then use the patent disclosure to push the frontiers of science even further. Indeed, there is every indication that the availability of patent protection for isolated genes (and similar compositions of matter based on structures found in the human body) has fueled an explosion of innovation and biomedical advance. Thus, while a particular patent may temporarily preempt competition narrowly, the patent system promotes innovation and competition broadly. Of course, once the patent term expires, all are free to enjoy, commercialize, and improve the claimed inventions. The considerable public interest would not be well served by curbing patent protection at a time when the horizons of science have expanded by looking inward, to human biology, as part of a new age of innovation—the Biotech Age.

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[6] The investment required for biologic treatments can reportedly exceed $1 billion, and is still rising. *See* Press Release, Tufts Center for the Study of Drug Development, Rising Clinical Trial Complexity Continues to Vex Drug Developers (May 5, 2010), *available at* http://csdd.tufts.edu/news/complete_story/pr_ir_may-jun_2010; Tufts Center for the Study of Drug Development, *Research Milestones: Drug Policy and Strategy Analyses to Inform R&D and Strategic Planning Decisions*, http://csdd.tufts.edu/research/research_milestones (last visited Jan. 22, 2013)(referring to a 2006 study that estimated the average cost of developing a new biotechnology product as $1.2 billion).

B. The Experimental Use Exception Allows For Some Uses of the Claimed DNA Molecules

In their brief on the merits, Petitioners argue that patent protection for Myriad's inventions "run[s] afoul of the First Amendment," "lock[s] up the body of knowledge" about BRCA1 and BRCA2, and will choke off "all study of them," which they allege conflicts with the Constitutional mandate that the patent law and policy should promote the progress of science and technology. Pet. Brief on the Merits, pp. 25, 40, 42.

These sweeping assertions are not true; they ignore the experimental use exception to a patent owner's exclusive rights. For nearly two centuries, the patent law has distinguished between experimenting "on" a patented invention for research or experimental purposes—which is not an infringing use—and using the invention for its stated purpose, thereby infringing the patent. *See Whittemore v. Cutter*, 29 F. Cas. 1120 (C.C.D. Mass.

1813)(No. 17,600); *Poppenhusen v. Falke*, 19 F. Cas. 1048, 1049 (C.C.S.D.N.Y.1861)(No. 11,279). This experimental use exception applies to non-commercial research, such as that conducted in not-for-profit university laboratories. *Cf. Madey v. Duke Univ.*, 307 F.3d 1351, 1361-62 (Fed. Cir. 2002). Moreover, Congress expressly provided for an experimental use exception to cover profit-related uses related to developing information for U.S. Food and Drug Administration submissions. 35 U.S.C. § 271(e)(1). Thus, there is substantial room for scientific inquiry into DNA sequencing, even as patent protection rewards the inventors by excluding others from exploiting commercial uses of their inventions.

The principle of a research or experimental exemption has a long history in patent law. By 1861, the law was "well settled[] that an experiment with a patented article for the sole purpose of gratifying a philosophical taste, or curiosity, or for mere amusement, is not an infringement of the rights of the patentee." *Poppenhusen*, 19 F. Cas. at 1049. As Justice Story noted in the mid-nineteenth century:

> [I]t could never have been the intention of the legislature to punish a man who constructed such a machine merely for philosophical experiments, or for the purpose of ascertaining the sufficiency of the machine to produce its desired effects.

Whittemore, 29 F. Cas. at 1121.

Furthermore, the Federal Circuit recognized the viability of this exception as recently as last year:

> [P]atenting does not deprive the public of the right to experiment with and improve upon the patented subject matter. As discussed in *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 142 (2001), "[t]he disclosure required by the Patent Act is 'the quid pro quo of the right to exclude,'" quoting *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 484 (1974). It is not necessary to wait for the patent to expire before the knowledge contained in the patent can be touched.

In re Rosuvastatin Calcium Patent Litig., __ F.3d ___, 2012 WL 6217356, at *12 (Fed. Cir. Dec. 14, 2012). As academics have noted, the experimental use exception should apply equally to genomic inventions. *See* J.M. Mueller, *Facilitating Patent Access to Patent-Protected Genetic Testing*, 6 J. Bus. & Tech. L. 83, 95 (2011)(footnotes omitted).[7]

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[7] For a detailed history and analysis of the experimental use exception, *see* R. E. Bee, *Experimental Use as an Act of Patent Infringement*, 39 J. Pat. Off. Soc'y 357 (1957) and L.C. Bruzzone, *The Research Exemption: A Proposal*, 21 AIPLA Q.J. 52 (1993).

The ability to perform research on a patented invention to understand the invention fosters further development and promotes the progress of the useful arts related to human genetics.

IV. Congress Has Recognized The Patent Eligibility of Isolated DNA Molecules

Congress repeatedly has recognized the patentability of isolated DNA molecules as inventions. Absent a clear directive to the contrary, it would be inappropriate for this Court to conclude otherwise.

In 1996, Congress enacted section 287(c) of the Patent Act to preclude actions for damages or injunctive relief against a medical practitioner certain arising out of medical activities that would otherwise be infringing. In providing a detailed recitation of the acts and subject matter covered, Congress expressly recognized the existence of "biotechnology patent[s]." *See* 35 U.S.C. § 287(c)(2)(A)(iii). The Conference Report for that legislation states that a "biotechnology patent" "includes ... a patent on a process of making or using biological materials, including treatment using those materials, where those materials have been manipulated *ex vivo* at the cellular or molecular level" and includes "genetic materials, such as DNA and RNA that is obtained from within the cell." H.R. Conf. Rep. No. 104-863, at 855. It also explains that this term refers to *ex vivo* manipulation, which includes the "propagation, expansion, selection, purification, pharmaceutical treatment, or alteration of the biologic characteristics of these substances outside of a human body." *Id.*; *see Chakrabarty*, 447 U.S. at 315 ("Congress, not the courts, must define the limits of patentability.").

Similarly, the Patent and Trademark Office has acted on this Congressional intent to grant thousands of patents claiming isolated DNA sequences and their use, and the biotechnology industry has long relied upon them. *See, e.g.*, Pet. App. 87a-89a (Moore, J., concurring-in-part). This Court should not change this interpretation of the patent statute without a "clear and certain signal from Congress." *Deepsouth Packing Co. v. Laitram Corp.*, 406 U.S. 518, 531 (1972). Indeed, with issues surrounding so-called "gene patents" in the forefront of scientific and policy debate, Congress recently amended the patent law, enacting the America Invents Act ("AIA"). Yet, in passing this sweeping overhaul of patent law, Congress did not exclude isolated DNA molecules from the scope of section 101. Indeed, rather than exclude DNA-related patents in the AIA, Congress explicitly recognized their existence. Pub. L. No. 112-29, § 27(a), 125 Stat. 338 (2011)(referring to "gene patents" in the context of requiring a study on genetic testing).

Both *Warner-Jenkinson Co. v. Hilton Davis Chemical Co.*, 520 U.S. 17, 28 (1997) and *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002), cautioned courts not to upset the settled expectations of the patent community absent a clear directive from Congress. In developing what is, literally, a multi-billion dollar industry, the U.S. biotechnology industry has relied on both Congressional action and inaction. The U.S.

biotechnology industry has led the field in the global economy in large part due to strong patent protection of DNA-based inventions. Such patent protection is critical to attracting investments and recouping the significant up-front expenditures for the type of skill, hard work, and ingenuity required to create and develop inventions such as those claimed in this case. *See* Melissa Wetkowski, *Unfitting: Gene Patent Limitations Too Tight For United States' Biotechnology Innovation and Growth in Light of International Patenting Policies*, 16 Sw J. Int'l L. 181, 198-99 (2010).

A ruling such as the one Petitioners seek in this case that isolated DNA molecules are not eligible for patent protection would deter investment in the biotechnology industry and put hard-won competitive market positions at risk. Worse, such a ruling would signal to inventors and investors working in other emerging biotechnologies that they cannot rely on the incentives and protections that have inspired and rewarded innovators from the earliest days of our republic. And, more devastatingly, it would not incentivize investors to look for new cures and diagnostics for disease. Given the stark effect such an abrupt change in the law would have on American biotechnology ingenuity and industry, Congress, not the courts, should initiate any dialogue about whether this settled law should be modified. *See* Nikos C. Varsakelis, *The Impact of Patent Protection, Economy Openness and National Culture on R&D Investment: A Cross-Country Empirical Investigation*, 30 Res. Pol'y 1059, 1066 (2001).

In this context, it is important to consider that: (1) patents have been granted on human genetics for a long time; (2) Congress has recognized and considered the availability of such protection and has chosen not to limit it in the context of enacting legislation; and (3) businesses are entitled to rely not only on Congressional action but also on Congressional inaction.

A. Moral and Ethical Considerations Are for Congress, Not the Courts

Those challenging Myriad's patents have invoked additional societal, moral, and ethical issues surrounding the exclusionary effects of purified, isolated DNA molecule patents. AIPLA is not unmindful of or unsympathetic to these concerns, but they require careful scrutiny in an appropriate forum.

Indeed, these issues, while important, are expressly reserved for Congress, not the courts, under its authority to enact laws that promote the progress of the useful arts. There has never been a "medical treatment/diagnostics" exception to Section 101. In fact, current patent policy should and does follow the Constitutional mandate to promote the next new advance lest researchers lack incentive to provide diagnostics and treatments because there is no protection for their inventions. And where Congress has spoken and set forth broad categories of patent-eligible subject matter, the courts should not narrow the scope of the patent laws based on their own balancing of ethical and moral considerations. *See Charkrabarty*, 447 U.S. at 317-

18 ("[U]ntil Congress takes [] action, this Court must construe the language of § 101 as it is.").

CONCLUSION

For the foregoing reasons, AIPLA urges the Court to affirm the judgment of the court of appeals.

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AMICUS
CURIAE
BRIEF

Supreme Court, U.S.
FILED
JAN 29 2013
OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,
Petitioners,

v.

MYRIAD GENETICS, INC., ET AL.,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF *AMICI CURIAE* AMERICAN MEDICAL ASSOCIATION, AMERICAN SOCIETY OF HUMAN GENETICS, AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS, AMERICAN OSTEOPATHIC ASSOCIATION, AMERICAN COLLEGE OF LEGAL MEDICINE, AND THE MEDICAL SOCIETY OF THE STATE OF NEW YORK IN SUPPORT OF PETITIONERS

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STATEMENT OF INTEREST OF *AMICI CURIAE*[1]

Amici are organizations of health care professionals. Their members number in the hundreds of thousands and they provide health care across the country.

Genetic information is integral to health care professionals' determination of which diseases a patient might be suffering from and which treatments might benefit or harm that patient. Patents on human genes interfere with health care professionals' ability to provide appropriate care to their patients. These patents inhibit, rather than encourage, scientific research and technological innovation. These adverse effects could and should have been avoided because human genes are not patentable subject matter.

Amicus Curiae **American Medical Association (AMA)**, a non-profit organization, is the largest professional association of physicians, residents, and medical students in the United States. The AMA joins this brief on its own behalf and as a representative of the Litigation Center of the American Medical Association and the State Medical Societies.

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[1] No counsel for a party authored this brief in whole or in part, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No party or entity other than *amici*, their members, or their counsel, made a monetary contribution to this brief's preparation or submission. Counsel of record received timely notice of the intent to file this brief under Supreme Court Rule 37. Petitioners have filed a letter with the Clerk of the Court granting consent to the filing of any and all *amicus curiae* briefs. Respondents' consent has been filed with the Clerk of the Court.

Amicus Curiae **American Society of Human Genetics (ASHG)** is a non-profit organization of over 8,000 professionals in the field of human genetics including researchers, clinicians, academicians, and counselors.

Amicus Curiae **American College of Obstetricians and Gynecologists (ACOG)** is a non-profit organization of over 55,000 health care professionals dedicated to providing quality health care to women. Over 90% of Board-certified obstetricians and gynecologists in the U.S. are affiliated with ACOG.

Amicus Curiae **American Osteopathic Association (AOA)**, with over 44,000 members, is the largest professional association of osteopathic physicians. The AOA promotes osteopathic medicine, a holistic approach to prevent, diagnose, and treat illness, disease, and injury.

Amicus Curiae **American College of Legal Medicine (ACLM)** is a non-profit professional society comprised primarily of members holding degrees in both medicine and law. The ACLM serves medical and legal professionals and advises health policymakers.

Amicus Curiae **Medical Society of the State of New York (MSSNY)** is a voluntary association of approximately 21,000 licensed physicians, residents, and medical students in all specialties in New York.

SUMMARY OF THE ARGUMENT

Patents on human genes impede the provision of health care, thwart public health objectives, shackle innovation, and violate ethical tenets. Patents are not needed to create an incentive for the discovery of human genes, and patent law does not exist to reward such scientific and medical discoveries.

Human gene patents—in this case, Myriad's claims over isolated DNA and cDNA—conflict with this Court's jurisprudence on subject matter patent eligibility, which holds that "laws of nature, natural phenomena, and abstract ideas" are not patentable subject matter. *Mayo Collaborative Services v. Prometheus Labs,* 132 S. Ct. 1289, 1293 (2012).

Myriad did not invent the DNA sequences covered by its patents; it has only removed them from people's bodies and taken them out of the cellular environment using common, long-standing techniques. Nor has Myriad invented any chemical or mechanical methods of determining whether there is a mutation in a breast cancer gene. Rather, what the patentee claims to have discovered are pre-existing, naturally-occurring genetic sequences and a natural relationship between certain mutations and breast cancer.

Myriad now suggests that even if its claims do not meet the requirements of patent law, the claims should be held valid due to reliance on long-standing patent practice. This argument is both factually and legally flawed. At the time Myriad sought its patent, the scientific and legal communities were in agreement that patents on genetic sequences were legally inappropriate and morally indefensible.

Are human genes patentable? Human genes are products of nature. Neither the breaking of the chemical bonds that incorporate specific sequences into the full genome nor the removal of non-coding regions from the naturally occurring gene create a new, markedly different composition of matter that merits the protection of patent law.

ARGUMENT

I. PHYSICIANS' AND RESEARCHERS' ACCESS TO HUMAN GENE SEQUENCES IS VITAL TO HEALTH CARE AND RESEARCH.

A person's genetic sequences hold a vast array of information relevant to his or her health. They can indicate a predisposition to disease, as well as pinpoint a diagnosis and provide guidance regarding what treatments might be beneficial (or risky) for that person. Genetic sequence information can mean the difference between life and death in the diagnosis and treatment of patients.

The benefits of genetic testing are not limited to people with rare diseases. Genetic factors contribute to the leading causes of death: cancers of all types, heart disease, hypertension, Alzheimer's, diabetes, susceptibility to infectious diseases (e.g. the flu), kidney disease, and asthma. Richard A. King, Jerome I. Rotter, and Arno G. Motulsky, The Genetic Basis of Common Diseases (2d ed. 2002). Even with respect to the narrow range of diseases that do not have a known genetic component, genetic testing has a role in determining how well patients will metabolize and respond to proposed medications.

Francis Collins, now director of the National Institutes of Health, said:

> By 2020, the impact of genetics on medicine will be even more widespread. The pharmacogenomics approach for

> predicting drug responsiveness will be standard practice for quite a number of disorders and drugs. . . . By 2020, it is likely that every tumor will have a precise molecular fingerprint determined, cataloging the genes that have gone awry, and therapy will be individually targeted to that fingerprint.

Francis S. Collins and Victor A. McKusick, *Implications of the Human Genome Project for Medical Science*, 285 Journal of the American Medical Association 540, 544 (2001). The benefits of access to genetic sequences are extensive, but patents on human genes thwart the realization of these benefits.

A. Patents on Human Genes Interfere with Diagnosis and Treatment of Patients.

A patent on the genetic sequence of a human gene grants the patent holder complete control over the use of that sequence for the life of the patent. The patent holder can forbid health care providers from using even unpatented methods to learn the sequence of a patient's gene. The patent holder can demand whatever royalty it sets from the person who seeks to learn his or her genetic sequence or it can completely prohibit a person from learning his or her own sequence.

Gene patent holders have prevented physicians and laboratories from offering genetic testing for medical conditions such as breast cancer, hearing loss, Alzheimer's, Long QT syndrome, Canavan disease, leukemia, hemochromatosis, and neurodegenerative disorders. Secretary [of Health and Human Services]'s Advisory Committee on Genetics, Health, and Society, *Report on Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests*, 40-42 (2010) [hereinafter "SACGHS"]; Debra G.B. Leonard, *Medical Practice and Gene Patents: A Personal Perspective*, 77 Academic Medicine 1388 (Dec. 2002).

Myriad's patents on the BRCA1 and BRCA2 gene sequences give it exclusive control over all previously and subsequently discovered means of testing for inheritable BRCA1 and BRCA2 breast cancer mutations. Myriad's exclusive control has led to the misdiagnosis of patients and has precluded the deployment of improved genetic tests. Tom Walsh et al., *Spectrum of Mutations in BRCA1, BRCA2, CHEK2, and TP53 in Families at High Risk of Breast Cancer*, 295 Journal of the American Medical Association 1379, 1386 (2006) (12% of the 300 people examined from high risk families had mutations that the Myriad tests missed).

The patenting of the BRCA1 and BRCA2 genes in the United States means that Americans must undergo tests that are inferior to and more costly than those available in other countries. In France, for example, a physician found a breast cancer gene mutation in an American family that the Myriad test had missed. Sophie Gad et al., *Identification of a Large Rearrangement of the BRCA1 Gene Using Colour Bar Code on Combed DNA in an American*

Breast/Ovarian Cancer Family Previously Studied by Direct Sequencing, 38 Journal of Medical Genetics 388, 389 (2001). Similarly, in countries where the Alzheimer APOE gene sequence and the hemochromatosis gene sequence were *not* patented, researchers found previously unknown mutations. *Gene Patents and Other Genomic Inventions: Hearings Before the Subcommittee on Courts and Intellectual Property of the House Committee of the Judiciary*, 106th Congress, 121-127 (2000) (statement of Dr. Jon F. Merz). If Myriad's patent claims over the BRCA1 and BRCA2 genes are invalidated, competition from other laboratories would allow the development of better tests. Swisher Decl. ¶¶ 24-26.

In this case, because Myriad has exclusive use of the BRCA1 and BRCA2 gene sequences, no woman in America can get an independent second opinion about her condition before deciding to have her healthy breasts or ovaries removed in order to avoid cancer. As a result, women may have their breasts or ovaries removed unnecessarily when they receive a false positive result on a BRCA1 or BRCA2 test because they do not have access to an independent confirmatory test. *See, e.g.*, Judy Peres, *Genetic Testing Can Save Lives – But Errors Leave Scars*, Chicago Tribune, September 26, 1999, at 1. Even when surgery is not performed, a false positive result could lead to a lifetime of medical testing and prophylactic treatment and fear that other family members may also be at risk for cancer. Myriad's exclusive control of the BRCA1 and BRCA2 gene sequences also restricts men's access to diagnostic testing. Although breast cancer is rarer in men, mutations in the BRCA genes of men do increase the risk of male breast cancer as well as prostate and pancreatic cancer.

Patents on genetic sequences have even led to the death of patients, as in the case of Long QT syndrome, a disorder of the heart's electrical system that is characterized by irregular heart rhythms and a risk of sudden death. The disease can be treated with an implanted defibrillator. A genetic sequence associated with Long QT was patented and assigned to the University of Utah Research Foundation. U.S. Patent No. 6,207,383. For a two-year period, the exclusive licensee did not offer diagnostic testing for Long QT syndrome. Other laboratories had the capability and willingness to assess whether patients had a potentially fatal mutation of the Long QT gene, but were prevented from doing so due to the patent on the genetic sequence. During this period at least one patient, a 10-year-old girl, died from undiagnosed Long QT syndrome. Her death could have been prevented if the isolated genetic sequence had not been patented. *Stifling or Stimulating – The Role of Gene Patents in Research and Genetic Testing: Hearing Before the Subcommittee on Courts, the Internet and Intellectual Property of the House Judicary Committee*, 110th Congress 40 (2007) (statement of Dr. Marc Grodman).

The promise of pharmacogenomics—the ability to test a patient's genetic sequence to determine whether a treatment might be helpful or deadly—has also been undermined by the patenting of genetic sequences. A company filed for patent protection on a genetic sequence that indicates whether patients will benefit from its asthma drug. For the 20-year term of the patent, the company will not allow anyone to analyze any patient's version of that gene sequence to determine whether its asthma drug will help or harm patients. Geeta Anand, *Big Drug Makers Try to Postpone Custom Regimens*, The Wall Street Journal, June 18, 2001, at B1. Even though such information is crucial to physicians and patients, the use of the sequence to identify people who would not benefit from a drug would diminish the market for the drug.

Patents on genetic sequences also interfere with multiplex testing, where the sequences of several genes (or even a person's entire genome) are tested at once. SACGHS at 49. For example, as many as 80 genes can indicate a predisposition to asthma. G. Malerba and P.F. Pignatti, *A Review of Asthma Genetics: Gene Expression Studies and Recent Candidates*, 46 Journal of Applied Genetics 93 (2005). For a complete diagnosis, all the relevant genetic sequences could be analyzed in one test. But genetic sequence patents preclude a single test from being used. Because some genetic sequence patents are exclusively licensed, a patient's tissue sample must be sent to multiple laboratories, increasing costs and introducing additional chances of error.

B. Patents on Human Genes Increase the Cost of Genetic Testing.

Patents on gene sequences unnecessarily increase the costs of health care, making genetic tests inaccessible for many people and imposing costs on others of unnecessary medical procedures due to false positive results. Because of the ability to charge royalties under patents on the BRCA1 and BRCA2 breast cancer genes, Myriad's test costs $3,000 (Answer to Complaint at 12 (S.D.N.Y. Nov. 20, 2009)), despite the existence of other laboratories willing to offer testing for one third of that cost. *Ontario to Offer New Genetic Test for Breast, Ovarian Cancer*, CBC News, Jan. 8, 2003, http://www.cbc.ca/health/story/2003/01/06/test_genetic030106.html. Patents on the Long QT genes drove the cost of the test to $5,400, when the test could have easily been undertaken for 75% less. Grodman, *supra,* at 39.

The technology exists to allow the sequencing of a person's entire genome of approximately 20,000 genes at an affordable rate, so that the person could take steps to prevent the disease. "The goal of completely sequencing a human genome for $1,000 is in sight." W. Gregory Feero, Alan E. Guttmacher, and Francis S. Collins, *Genomic Medicine – An Updated Primer*, 362 New England Journal of Medicine 2001, 2008 (2010). However, patents on genetic sequences impede the deployment of a whole genome analysis for patients. Sulston Decl. ¶ 38; Ledbetter Decl. ¶ 24. Technologies suitable for whole genome analysis require the use of isolated gene sequences. *See, e.g.,* Pauline C. Ng and Ewen F. Kirkness, *Whole Genome Sequencing,* 628 Methods Molecular Biology 215, 216 (2010). Even under the conservative estimate that 3% of existing gene sequence claims would block genetic diagnostic testing, "a full-genome sequence analysis would still infringe several hundred patents." Robert Cook-Deegan and Christopher Heaney, *Patents in*

Genomics and Human Genetics, 11 Annual Review of Genomics and Human Genetics 383, 414 (2010).

Testing all 20,000 of a person's genes at the Myriad BRCA rate would convert a test that could be done for $1000 to one that cost over $37 million. Applying even a seemingly modest royalty of $100 per gene would result in an unaffordable $2 million royalty per test. If the decision of the Court of Appeals for the Federal Circuit is upheld, physicians will be unable to provide meaningful analysis and comprehensive genetic information to patients.

C. Patents on Human Genes Impede Innovation.

Patents on "isolated" DNA impede innovation. Any research or diagnosis done on a gene from a patient's body is controlled by the patent holder because research and diagnosis cannot be undertaken without "isolating" the DNA from the body. Myriad has stopped research involving BRCA1 and BRCA2 at major universities such as Yale. Kimberly Blanton, *Corporate Takeover Exploiting the US Patent System,* Boston Globe Magazine, Feb. 24, 2002, at 10.

Myriad has misrepresented the ability to invent around its patent claims by arguing that there are alternative technologies for determining a patient's predisposition to developing breast and ovarian cancer that do not involve the use of isolated DNA. Myriad Br. at 26 (S. Ct. Oct. 31, 2012). Myriad claims that random ("shotgun") sequencing, single-molecule sequencing, nanopore sequencing, protein truncation testing, and gene expression profiling can be performed without infringing Myriad's patent claims. Myriad Br. at 5-7 (S. Ct. Oct. 31, 2012). However, each of these technologies requires the use of isolated DNA controlled by Myriad's patents.

The term "isolated" is defined broadly in Myriad's patents: "the term embraces a nucleic acid sequence or protein which has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems." U.S. Patent No. 5,747,282. The technologies cited by Myriad require that a DNA sequence is removed from its naturally occurring environment during sequencing, that a DNA sequence separate from its naturally occurring environment is assembled during sequencing, or that cDNA is used while testing for an expression profile. Pauline C. Ng and Ewen F. Kirkness, *Whole Genome Sequencing*, 628 Methods Molecular Biology 215, 216 (2010); John Eid et al., *Real-Time DNA Sequencing from Single Polymerase Molecules,* 323 Science 133 (2008); Johan T. Den Dunnen and Gert-Jan B. Van Ommen, *The Protein Truncation Test: A Review*, 14 Human Mutation 95, 96 (1999); Asher Y. Salmon et al., *Determination of Molecular Markers for BRCA1 and BRCA2 Heterozygosity Using Gene Expression Profiling*, 6 Cancer Prevention Research 1, 2 (2013). All those approaches are covered by the Myriad patent claims.

Patents on human genes in general, and Myriad's patents in particular, thwart rather than promote innovation. Over half (53%) of laboratory directors say they have been impeded from developing tests due to gene patents. Cho Decl. ¶ 10; Mildred K. Cho et al., *Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services*, 5 Journal of Molecular Diagnostics 3 (2003). Moreover, in the face of threats and the potential costs of a suit for patent infringement, researchers may elect to use limited resources elsewhere rather than build on already useful research. This sort of over-deterrence hinders the normal process of scientific advances.

Patent law is supposed to be a bargain in which the patent holder gets a time-limited exclusive right to make, use, or sell a claimed invention of proportional scope to the inventive contribution to the field, in exchange for publishing in the patent the description of the invention that all can use to further develop the frontiers of science and technology. *See generally* Suzanne Scotchmer, *Standing on the Shoulders of Giants: Cumulative Research and the Patent Law*, 5 Journal of Economic Perspectives 29 (1991). However, the system breaks down when a patent is granted for information itself—such as the sequence of a gene. That patent gives the holder a right to prevent others from using the disclosed information entirely.

D. Existing Non-Patent Incentives Are Sufficient to Encourage Innovation in Genetics.

Myriad argues that patents are necessary to encourage innovation (such as the discovery and isolation of genetic sequences). Myriad Supp. Br. at 16-18 (Fed. Cir. June 15, 2012). But the majority of geneticists are willing to undertake the research to discover genes and develop genetic tests without the possibility of a patent. In fact, in a study of ASHG members, 61% of those in industry, 78% of those in government, and 77% of academic scientists stated that they disapproved of patenting DNA. Isaac Rabino, *How Human Geneticists in U.S. View Commercialization of the Human Genome Project*, 29 Nature Genetics 15 (2001).

"[P]atents were not needed to develop genetic tests for hearing loss, SCA [spinocerebellar atrophy], breast cancer, LQTS [long-QT syndrome], Canavan disease, and HH [hereditary hemochromatosis]. Indeed, all of these tests were on the market before the test offered by the relevant patent-rights holder." SACGHS at 31.

Amici supporting Myriad also assert that patents are needed to promote genetic innovations. Amici Curiae Br. for Biotechnology Industry Organization and Association of University Technology Managers at 4 (Fed. Cir. Oct. 29, 2010) ("BIO Br."); Amicus Curiae Br. for Pharmaceutical Research and Manufacturers of America at 17 (Fed. Cir. Oct. 24, 2010). However, none of these *Amici* provide any actual evidence that the possibility of obtaining gene patents was necessary for the discovery of gene sequences and their correlation to breast cancer or other diseases, or for the discovery of new diagnostics or treatments for those diseases. In fact, the examples cited by these *Amici* prove the harm that such patents have caused. For example, *Amicus* BIO argues that the patenting of the hepatitis C genome was a success story. *See* BIO Br. at 20. But it actually has been a disaster for public health because the patent holder blocked the deployment of an inexpensive effective test developed by a small biotechnology company and, as a result, many patients have not been tested or received timely treatment. Letter from Martin Munzer to Xavier Becerra, U.S. Congressman (May 25, 2007).

Similarly, Myriad argues that the Taxol patent proves that patents on isolated products of nature are necessary for beneficial therapeutics to reach the market. Appellants' Br. at 46 (Fed. Cir. Oct. 22, 2010). But Myriad is clearly mistaken, since patents were never granted on the compound isolated from the yew tree (Taxol), but only on a means of administering it. Ken Garber, *Battle Over Generic Taxol Concludes, But Controversy Continues*, 94 Journal of the National Cancer Institute 324 (2002); U.S. Patent No. 5,641,803; U.S. Patent No. 5,670,537. Furthermore, even if there had been a patent on the isolated compound, it would not prove that the research to isolate Taxol required the patent incentive.

Even the genetic sequences at issue in this case would have been discovered without the patent incentive. The international Breast Cancer Linkage Consortium was fully engaged in identifying the BRCA1 gene in a cooperative effort and planned to make the sequence publicly available and not to patent it. Jordan Paradise, *European Opposition to Exclusive Control Over Predictive Breast Cancer Testing and the Inherent Implications for U.S. Patent*

Law and Public Policy, 59 Food & Drug Law Journal 133, 143-144 (2004); Phyllida Brown & Kurt Kleiner, *Patent Row Splits Breast Cancer Researchers*, New Scientist, Sept. 24, 1994, at 44. The publicly-funded consortium did most of the work to identify the BRCA1 gene, but shortly before it completed its work, Mark Skolnick, a member of the consortium, founded Myriad Genetics, and sought a patent on the BRCA1 gene, in violation of the goals of the Consortium. Paradise at 143.

Skolnick utilized over $5 million of taxpayer money (a grant from the National Institutes of Health) and relied on the aid of federal researchers to sequence the BRCA1 gene. Bryn Williams-Jones, *History of a Gene Patent: Tracing the Development and Application of Commercial BRCA Testing*, 10 Health Law Journal 123, 131 (2002). Rachel Nowak, *NIH in Danger of Losing Out on BRCA1 Patent*, 266 Science 209 (1994). The public thus paid for the work underlying Myriad's patents, yet is paying over $400 million more in royalties each year because of the patents at issue here.[2] If Skolnick had not sought the patent, the gene sequence would have been placed in the public domain.

A similar situation occurred with BRCA2. Myriad collaborated with Dr. Michael Stratton of the Institute for Cancer Research, London, and other researchers. Stratton ended the collaboration upon learning of Myriad's plans to patent the gene. The day after Myriad filed its patent for the BRCA2 gene, the Stratton group published its identification of the BRCA2 gene in the journal Nature. Richard Wooster, et al., *Identification of the Breast Cancer Susceptibility Gene BRCA2,* 378 Nature 789 (1995). As the district court pointed out, "the consensus among the scientific community is that the Stratton group, rather than Myriad, was the first to sequence the *BRCA2* gene." *Association for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F. Supp. 2d 181, 202 (S.D.N.Y. 2010). *See also* Robert Dalpé et al., *Watching the Race to Find the Breast Cancer Genes,* 28 Science, Technology, and Human Values 187 (Apr. 2003). Thus, the Myriad patents were not necessary for the discovery of these genes.

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[2] In 2012, Myriad spent $51,500,000 to perform molecular diagnostic tests, and gained revenue for their tests totaling $472,390,000. Form 10-K, submitted by Myriad Genetics, Inc., Commission file number: 0-26642, at 44 and F-3.

II. MYRIAD'S CLAIMS ARE INVALID UNDER SECTION 101 JURISPRUDENCE AND UNDER ARTICLE I, SECTION 8, CLAUSE 8 OF THE U.S. CONSTITUTION.

Nature's handiwork is excluded from patentability. *Mayo Collaborative Services v. Prometheus Labs,* 132 S. Ct. 1289, 1293 (2012); *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010). "'Laws of nature, natural phenomena, and abstract ideas' are not patentable." *Mayo*, 132 S. Ct. at 1293 (citations omitted). "[A] new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter." *Id.*; *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) (citing *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948). Rather, a newly discovered natural phenomenon must be "treated as though it were a familiar part of the prior art" and free for all to use. *Parker v. Flook*, 437 U.S. 584, 591-92 (1978). *See also Bilski v. Kappos*, 130 S. Ct. 3218, 3230 (2010).

Even when a newly-discovered law of nature or product of nature is novel, nonobvious, and useful, it is still not patentable under Section 101. *Mayo*, 132 S. Ct. at 1304. Nor can a patent be granted on a synthetic product that is not markedly different from what is found in nature. *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 311 (1884).

To be valid, a claimed invention involving a product of nature must have an inventive concept that involves significantly more than describing the product of nature. The claimed invention must be "markedly different" from what occurs in nature.[3] *Chakrabarty*, 447 U.S. at 310. *See also Funk Bros.*, 333 U.S. at 130; *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1, 11-12 (1931); *Cochrane*, 111 U.S. at 311.

Section 101 of the Patent Act, 35 U.S.C. § 101, ensures that innovators in our society—including physicians and scientists—have access to the raw materials for innovation. Laws of nature and products of nature are the "basic tools of scientific and technological work." *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972). Innovation is enhanced when all researchers have access to these basic tools.

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[3] This test is no more difficult to apply than any other analysis of patentability. If an inventor patents one type of mousetrap and another inventor files for a patent on another type of mousetrap, a judgment must be made about whether the second mousetrap involved an inventive concept and was markedly different from the prior art (the first mousetrap). In the application of Section 101, a similar analysis is made. But in that case the prior art is the product of nature itself.

The patent claims at issue in this case, covering isolated DNA and cDNA which are described by their genetic sequences, are invalid because they are patents on products of nature without an inventive concept and because isolated DNA and cDNA are not markedly different from what occurs in nature in every human being

Allowing Myriad's claims to stand would be inconsistent with the goals of the patent clause of the U.S. Constitution and the policies that have been part of the Patent Act since its inception. The drafters of the Constitution sought to give Congress the power to promote the widespread distribution of knowledge in the most effective way possible. The U.S. Constitution, Article I, Section 8, Clause 8, grants Congress the power to provide inventors time-limited exclusive rights over their inventions in order "to promote the progress of Science and the useful Arts." However, patents for human genetic material directly threaten that idea, essentially blocking future research and development and stopping science in its tracks.

Since the inception of the patent system, products of nature and laws of nature have been excluded from patentability. Writing in 1889, a patent law scholar noted that someone "may invent a machine, and may discover an island or law of nature. For doing the first of these things, the patent laws may reward him, because he is an inventor in doing it; but those laws cannot reward him for doing either of the others, because he is not an inventor in doing either." Albert A. Walker, *Text-Book of the Patent Laws of the United States of America* 2-3 (L. K. Strouse & Co., 2d ed. 1889). Myriad is not an inventor under patent law and should not have been allowed to claim patents on isolated DNA and cDNA.

A. Isolated DNA Is an Unpatentable Product of Nature.

Myriad has not invented the genes that exist naturally in people's bodies; it has only removed them from those bodies and taken them out of the cellular environment, using common, long-standing techniques. Beginning in 1869, scientists learned to isolate DNA from the body by removing it from the rest of the cellular material. Ralf Dahm, *Discovering DNA: Friedrich Miescher and the Early Years of Nucleic Acid Research*, 122 Human Genetics 565-581, 567-8 (2008) (documenting the activities of Dr. Miescher). A century later, in the 1970s, scientists could not only isolate DNA from the cell but could also synthesize DNA. Jeffrey Ross et al., *In Vitro Synthesis of DNA Complementary to Purified Rabbit Globin mRNA*, 69 Proceedings of the National Academy of Sciences 264 (1972).

Myriad claims that its inventive step was isolation of the BRCA1 and BRCA2 genes. Yet, as the Federal Circuit stated in *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, "isolation of interesting compounds is a mainstay of the chemist's art," and "[i]f it is known how to perform such an isolation doing so 'is likely the product not of innovation but of ordinary skill and common sense.'" 499 F.3d 1293, 1302 (Fed. Cir. 2007) (quoting *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)).

Nor does the breaking of covalent bonds make isolated DNA patentable. The breaking of covalent bonds (itself a natural process that occurs in the body) is not an "inventive concept" and does not make the gene sequence "markedly different" and therefore patentable subject matter. The change in chemical bonds is insignificant because the isolated gene sequence is the same string of nucleotides that exists in the cell. In fact, the sequences patented by Myriad would be of no use in diagnosis or treatment if they were different from the sequences that occur naturally in the human body. Additionally, because the claims are written in terms of the genetic sequences, patentability should be determined by an analysis of the genetic sequence, not by the chemical structure and its relation to covalent bonds. Moreover, it makes no sense to have patentability turn on the issue of whether covalent bonds are broken, since DNA that is not covalently bonded exists in the body and since the other bonds (such as hydrogen bonds) are actually more important than covalent bonds in terms of DNA functioning. Amici Curiae Br. for Academics in Law, Medicine, Health Policy and Clinical Genetics (S. Ct. Oct. 26, 2012).

Finding a gene is like finding a new plant in the wild, even if isolated from surrounding flora. To allow a patent on a gene "isolated" from the body is akin to allowing the first surgeon who removed a kidney to patent any and all "isolated" kidneys.[4] The holder of the patent on an isolated kidney could prevent other surgeons from removing ("isolating") diseased kidneys. The patent holder could also use its exclusive rights to charge a royalty of $3,000 or more each time a person donated a kidney to a relative.

B. cDNA Is an Unpatentable Product of Nature.

Every gene contains exons (sequences which direct the production of proteins) and introns (sequences which do not code for the creation of proteins). cDNA (complementary DNA) is the DNA sequence of a gene with the non-coding regions removed. cDNA is useful because it has the same nucleotide sequence and contains the same information as the coding regions of naturally occurring genes and can perform the same functions as a full genetic sequence or DNA molecule. Bruce Alberts et al., Molecular Biology of the Cell 469-546 (4th ed. 2002).

cDNA is not "markedly different" from the sequences that occur naturally within the chromosome. Myriad's use of routine techniques to isolate the coding regions of the BRCA1 and BRCA2 sequences lacks the inventive concept necessary for patentable subject matter.

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[4] When Myriad's counsel was pressed to identify its inventive concept at oral argument on remand, Myriad's main argument was that the decision of the scientist about where to "cut" the gene sequence to remove it from the chromosome was the inventive concept. Fed. Cir. Oral Arg. on Remand Trans. at 42:48 (July 20, 2012). Under such logic, the first surgeon who successfully removed a kidney for transplant, because he decided where to cut, could obtain a composition of matter patent covering all kidneys later removed by anyone else.

In *Funk Brothers,* the patent applicant isolated certain naturally-occurring bacteria and combined them in a novel and useful way, yet this did not convert the bacteria from ineligible "phenomena of nature" to eligible inventions. 333 U.S. at 130. To permit the patent would have required "allowing a patent to issue on one of the ancient secrets of nature now disclosed." *Id.* at 132. With respect to cDNA, in combining naturally-occurring exons, each exon, like each bacteria in *Funk Brothers*, "has the same effect it always had. . . . [and] perform[s] in [its] natural way." *Id.* at 131. "They serve the ends nature originally provided and act quite independently of any effort of the patentee." *Id.* Moreover, once the gene's naturally occurring DNA sequence—an unpatentable product of nature—is known, creation of cDNA is a routine mainstay of the art of biologists and chemists. Allowing a patent on cDNA would be a disproportionate reward in relation to what the alleged inventor contributed.

C. Synthetically Created Versions of Genetic Sequences Are Not Patent Eligible Inventions.

Even though none of its claims uses the term "synthesized," Myriad is apparently trying to avoid application of the products of nature doctrine by asserting that it is entitled to patents on the BRCA1 and BRCA2 genes because the claimed isolated DNA and cDNA were "synthesized." Appellants' Br. at 7 (Fed. Cir. Oct. 22, 2010); Myriad's Br. at 1 (S. Ct. Oct. 31, 2012). The process of synthesis, routinely done today by biology students, was not invented by Myriad, but is merely a way to make a copy of a whole gene or, in the case of cDNA, a copy of the sequences of the coding regions. The "synthesis" of DNA is the process of stringing together naturally existing nucleotides in the same order to function in the same way as the naturally occurring DNA. Michael J. Czar et al., *Gene Synthesis Demystified*, 27 Trends in Biotechnology 63 (2009). Synthesis occurs through the use of the naturally-occurring functions of DNA (such as annealing to its complementary strand), not because of some patent-worthy innovation of the scientist.

Synthetic substances are not patentable unless they are "markedly different" from the products of nature from which they derive. *Chakrabarty*, 447 U.S. at 310. In *Cochrane*, 111 U.S. at 311, the Supreme Court held that a patentee that had made and claimed a synthetic version of a naturally occurring dye (alizarine)—but having a brighter hue—did not claim a patent eligible invention but only an ineligible product of nature. "Calling it artificial alizarine *did not make it a new composition of matter, and patentable as such, by reason of its having been prepared artificially*." *Id.* (emphasis added).

Allowing patents on synthesized DNA would be inconsistent with policies that have been part of the Patent Act since its inception. The Patent Act of 1793, drafted by Thomas Jefferson, stated that "simply changing the form or the proportions of any machine, or composition of matter, in any degree shall not be deemed a discovery." Patent Act of 1793, Ch. 11, § 2, 1 Stat. 318-23 (Feb. 21, 1793).

Moreover, products of nature, abstract ideas, and laws of nature, must be "*assumed to be within the prior art*," even when their discovery by a patent applicant was the result of substantial investments and difficult scientific research efforts. *Bilski*, 130 S. Ct. at 3230 (quoting *Parker v. Flook*, 437 U.S. 584, 594 (1978) (emphasis added)); *O'Reilly v. Morse*, 56 U.S. (15 How.) 62, 115 (1853) (citing *Neilson v. Harford*, Web. Pat. Cases 295, 371 (1844)). Accordingly, even "synthetic" cDNA would reflect at most "token postsolution components" to the "prior art" natural DNA molecules and sequences. *Bilski*, 130 S. Ct. at 3231.

D. Myriad's Contributions Do Not Justify the Threat to Innovation.

In a Section 101 analysis, courts need to weigh "how much future innovation is foreclosed relative to the contribution of the inventor." *Mayo*, 132 S. Ct. at 1303. Indeed, "[t]he reason for the exclusion is that sometimes *too much* patent protection can impede rather than 'promote the Progress of Science and useful Arts.'" *Laboratory Corp. of America Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 126 (2006) (Breyer, J., dissenting). In *O'Reilly v. Morse*, this Court held that by patenting all uses of electromagnetism to produce characters at a distance, "while he shuts the door against inventions of other persons, the patentee would be able to avail himself of new discoveries in the properties and powers of electro-magnetism which scientific men might bring to light." 56 U.S. (15 How.) at 113. In this case, Myriad can improperly avail itself of all later discoveries related to human breast cancer genetic diagnosis and treatments, disproportionate to its efforts.

Myriad's contribution to the sequencing and identification of the BRCA1 and BRCA2 genes was minor in comparison to what its patents foreclose. Myriad used common techniques to isolate, sequence, and clone the BRCA1 and BRCA2 genes. The purported invention was not markedly different from the gene sequence in the body.

The core of the patents at issue is the discovery of a natural phenomenon—the sequence of a gene. But that discovery is not patentable since it was created by nature and occurs in every person's body. Once it is conceded that the gene sequence in the body cannot be patented, Myriad's action in isolating that sequence is minimal and not inventive.

Myriad not only patented the entire genetic sequence of BRCA1 and of BRCA2, but also every sequence of 15 nucleotides that appears in the BRCA1 genetic sequence. *See* claims 5 and 6 of U.S. Patent No. 5,747,282. These sequences appear hundreds of thousands of times in the 3 billion base pairs of the human genome. Myriad now can demand a royalty for the use of numerous genetic tests that have nothing to do with breast cancer because those sequences of 15 nucleotides occur in so many places in the genome. There are 340,000 infringing sequences on Chromosome 1 alone. Thomas Kepler, Colin Crossman, Robert Cook-Deegan, *Metastasizing Patent Claims on BRCA1*, 95 Genomics 312 (2010). Since those 15 nucleotide sequences occur an average of 14 times per gene, Myriad could ask for a royalty on every test done on any gene. Myriad could hold hostage the deployment of whole genome sequence testing by threatening to pursue an infringement action for every instance one of those 15 nucleotide segments is sequenced.

III. MYRIAD'S RELIANCE ARGUMENT IS INCONSISTENT WITH PATENT LAW AND IS NOT SUPPORTED IN FACT.

In 1995, when Myriad filed its first patents on the BRCA genetic sequences at issue in this case, the understanding in the medical, scientific and legal community was that a human gene sequence could not be and should not be the subject of intellectual property claims.

George Cahill, the Vice President of Scientific Training and Development at the Howard Hughes Medical Institute, pointed out that intellectual property claims on gene sequences would create an incentive to delay publication in contravention of scientific tradition. Leslie Roberts, *Who Owns the Human Genome?*, 237 Science 358 (1987). University of Washington professor Maynard Olson said, "it's like patenting the periodic table. To put patent value on cream skimming sends the wrong signal." Norton D. Zinder, *Patenting cDNA 1993: Efforts and Happenings*, 135 Gene 295 (1993).

Scientific and medical organizations across the world wrote that human genes did not—and should not—qualify for patentability. The Human Genome Organization, the international organization of genomic scientists, wrote in 1992 that "the human genome is our common heritage and collective property; genetic information is . . . in the public domain. . . . [H]uman DNA is not patentable, but belongs to humankind." Barbara Looney, *Should Genes Be Patented? The Gene Patenting Controversy: Legal, Ethical, and Policy Foundations of an International Agreement*, 26 Law & Pol'y Int'l Bus. 231, 239 (1994) (quoting Human Genome Organization, Ethical Implications of the Human Genome Project: International Issues 10 (1992)).

The World Medical Association declared that genetic information "should be general property and should not be used for business aims. Therefore no patents should be given for the human genome or parts of it." World Medical Association Declaration on the Human Genome Project Adopted by the 44th World Medical Assembly, Marbella, Spain, September 1992, reprinted in 87 Bulletin of Medical Ethics 9 (1993).

Science ministers in Europe took a stance against patenting genes. G. Kenneth Smith and Denise M. Kettelberger, *Patents and the Human Genome Project*, 22 American Intellectual Property Law Association Q.J. 27, 47-48 (1994). The French science minister, writing in the prestigious American research publication, Science, said:

> It would be prejudicial for scientists to

> adopt a generalized system of patenting knowledge about the human genome. This would increase costs and penalize low-budget research teams and countries with fragile economies. In addition, such a development would be ethically unacceptable. A patent should not be granted for something that is part of our universal heritage.

Hubert Curien, Letter, *The Human Genome Project and Patents*, 254 Science 1710 (1991).

The scientific, legal and medical literature prior to 1995 also indicated that gene sequences would likely fail to meet requirements for patentability. *See, e.g.* Joseph H. Nadeau, *Who Owns Our Genes?*, 27 Hospital Practice 12 (1992); N. Byrne, *Patents for Human Genes, Ownership of Biological Materials and Other Issues in Patent Law*, 199 World Patent Information 15 (1993); Barbara Looney, *Should Genes Be Patented? The Gene Patenting Controversy: Legal, Ethical, and Policy Foundations of an International Agreement*, 26 Law & Pol'y Int'l Bus. 231, 234 (1994).

A 1995 article in Medical Law International pointed out that patent law protection for Human Genome Project work was "neither desireable nor defensible." Philippa Gannon, Tom Guthrie and Graeme Laurie, *Patents, Morality and DNA: Should There Be Intellectual Property Protection of the Human Genome*, 1 Medical Law International 321, 337 (1995).

At the time the applications for the patents at issue in this case were filed, what Myriad had done was already quite ordinary. It was widely felt that, cDNA did not meet the requirements of patent law because "it is difficult to see any inventive activity" since "cDNA sequences . . . can now [in 1995] be generated relatively quickly by automatic sequencers." Philippa Gannon, Tom Guthrie and Graeme Laurie, *Patents, Morality and DNA: Should There Be Intellectual Property Protection of the Human Genome*, 1 Medical Law International 321, 337 (1995).

In 1992, James Watson, co-discoverer of the double-helix and the first director of the Human Genome Project, voiced his opposition to human gene patents. In his brief in this case, Watson explained, "A scientist does not—and should not—expect to obtain a legal monopoly controlling the information encoded by human genes. And the average scientist should not expect a windfall simply for revealing the sequence of DNA bases that encode various genes." Amicus Brief for James D. Watson in Support of Neither Party at 12-13 (Fed. Cir. June 15, 2012).

The genetics and legal community at the time of Myriad's patent applications acknowledged that intellectual property rights could be sought on therapeutics developed based on genetic knowledge, but that gene sequences themselves were not patentable subject matter. Hubert Curien, Letter, *The Human Genome Project and Patents*, 254 Science 1710 (1991).

Myriad claims it "relied on the certainty of patent protection" for isolated molecules at the time of filing its patents. Myriad's Br. at 2 (S. Ct. Oct 31, 2012). But there was no "certainty" at the time of filing its patents nor is there any now. Myriad was on shaky legal and moral ground when patenting genes, so its reliance argument is not meritorious. The United States Patent and Trademark Office had not even adopted guidelines about gene patents when Myriad sought the patents at issue in the case. Rather than being harmed by a detrimental reliance, Myriad for years has been unjustly enriched by the money it has made based on its patents on BRCA1 and BRCA2—patents that should never have been granted. *See generally Greenberg v. Miami Children's Hospital Research Institute, Inc.*, 264 F.Supp.2d 1064 (S.D. Fla. 2003).

IV. THE UNITED STATES PATENT AND TRADEMARK OFFICE ERRED IN GRANTING HUMAN GENE PATENTS AND ITS ERRONEOUS DECISION SHOULD NOT BE GIVEN DEFERENCE.

The United States Patent and Trademark Office (USPTO) ignored this Court's precedents and applied flawed reasoning to permit patents on genetic sequences. Consequently, that reasoning should not be accorded deference. In 2001, the USPTO relied on the 1873 grant of a patent to Louis Pasteur for a purified yeast and on a 1911 lower court decision upholding a patent for isolated and purified adrenaline. *Utility Examination Guidelines*, 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001); *Parke-Davis & Co. v. H. K. Mulford Co.*, 189 F. 95 (S.D.N.Y. 1911), *affirmed*, 196 F. 496 (2d Cir. 1912). However, the Pasteur patent and *Parke-Davis* preceded this Court's decision in *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1 (1931). That decision elaborated on the products of nature doctrine in a way that calls into question the grant of the yeast patent and adrenaline patent. Indeed, no less an authority than Pasquale J. Federico (later Commissioner of Patents and principal drafter of the 1952 Patent Act, which includes Section 101) stated that in light of *American Fruit Growers*, a claim like Pasteur's "would now probably be refused by the examiner, since it may be doubted that the subject-matter is capable of being patented." Pasquale J. Federico, *Louis Pasteur's Patents*, 86 Science 327 (1937).[5] Thus, the USPTO erred when it began granting patents on genetic sequences.

The Federal Circuit compounded this error by looking to *Parke-Davis* in assessing the genetic sequence claims. *Association for Molecular Pathology*, 689 F.3d at 1329; *see also id.* at 1339 (Moore, J., concurring-in-part). Judge Moore additionally cited the discredited Pasteur patent as precedent. *Id.* at 1333 (Moore, J., concurring-in-part).

The Federal Circuit also held that the

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[5] The Pasteur patent might not even have been valid according to the law at the time it was issued. Since Pasteur never enforced his patent, there was no judicial assessment of whether the patent was valid. Maurice Cassier, *Louis Pasteur's Patents: Agri-Food Biotechnologies, Industry and Public Good*, *in* Living Properties, 39 (Jean-Paul Gaudillière, *et al.*, eds., 2009).

USPTO's actions created "settled expectations" that prohibited the Federal Circuit from holding genetic sequence claims invalid. *Id.* at 1332-1333; *see also id.* at 1366-1367 (Moore, J., concurring-in-part). However, allowing settled expectations to dictate the validity of a patent would lead to absurd results. The examiners at the USPTO are not infallible. Sometimes whole categories of claims have been erroneously included or excluded from patentability. In fact, in a study of challenges to patent validity, 46% of challenged patents were found to be invalid. John R. Allison and Mark A. Lemley, *Empirical Evidence on the Validity of Litigated Patents*, 26 American Intellectual Property Law Association Q.J. 185 (Summer 1998).

If the USPTO were owed the level of deference that the Federal Circuit proposes, there would be no recourse to challenge invalid patents. Anytime a court reviews a patent there inevitably is a chance to change settled expectations. In *State Street Bank & Trust Co. v. Signature Financial Group, Inc.*, 149 F.3d 1368 (Fed. Cir. 1998), the Federal Circuit changed the settled expectation of business owners who had previously felt free to use business methods without concern for patent infringement. As is clear in *Mayo*, settled expectations do not provide an adequate reason for courts to uphold otherwise invalid patents. 132 S. Ct. at 1304-1305.

Furthermore, the U.S. Government asked the Federal Circuit not to give deference to the USPTO's practice of granting patents on isolated DNA. The Department of Justice submitted an *amicus* brief to the Federal Circuit arguing that isolated DNA is a product of nature and not patentable subject matter. Amicus Brief for the United States in Support of Neither Party at 11 (Fed. Cir. Oct. 29, 2010).

> The chemical structure of native human genes is a product of nature, and it is no less a product of nature when that structure is "isolated" from its natural environment than are cotton fibers that have been separated from cotton seeds or coal that has been extracted from the earth.

V. INVALIDATION OF HUMAN GENE PATENTS IS NOT ONLY REQUIRED BY SECTION 101 AND ARTICLE I, SECTION 8, CLAUSE 8 OF THE U.S. CONSTITUTION, IT IS CONSISTENT WITH SCIENTIFIC AND MEDICAL ETHICS CODES.

Scientists have long-standing, historically recognized duties to freely disseminate their discoveries of products of nature and laws of nature and not to subject those discoveries to private property rights. *See, e.g.*, Robert K. Merton, On the Shoulders of Giants: A Shandean Postscript (1985). Medical professionals, too, recognize the ethical duty to share scientific knowledge rather than to patent it.

Amicus AMA's Ethics Opinion 2.105, entitled "Patenting Human Genes," states, "One of the goals of genetic research is to achieve better medical treatments and technologies. Granting patent protection should not hinder this goal." Similarly, *Amicus* ACOG's ethics opinion finds medical and surgical patents to be unethical and urges that genetic sequence patents not be granted. The American College of Obstetricians and Gynecologists, *ACOG Committee Opinion Number 364: Patents, Medicine, and the Interests of Patients*, 109 Obstetrics & Gynecology 1249, 1252 (2007, reaffirmed 2009).

Just as patent law recognizes that discoveries of nature must be widely shared to promote innovation, physicians' and scientists' ethical duties recognize that laws of nature and products of nature must be treated as prior art and shared to benefit the public and to encourage innovation.

CONCLUSION

Under the U.S. Constitution Art. I, § 8, cl. 8, and 35 U.S.C. § 101, isolated genetic sequences are not patentable subject matter. The mere fact of isolation is not enough of a change from what exists in nature to find patentability, as the products *do not have any functions that they did not have already.* Similarly, "synthetic" genetic sequences that are not materially different from their naturally occurring counterparts are not patentable inventions.

Patents on gene sequences, including patents on isolated DNA and cDNA, harm patient care and the progress of science. They interfere with diagnosis and treatment, quality assurance, access to health care, and scientific and medical innovation. They prevent people from receiving appropriate individual health care and thwart public health initiatives.

Non-patent incentives are fully adequate to encourage scientific and medical innovation with respect to human genes. The examples supplied by petitioner's *Amici* only confirm the harms that the patent system causes when extended to genetic sequences.

The U.S. Government has now admitted that it erred in issuing thousands of isolated and purified sequence claims without possessing authority to do so. This error has imposed untold costs on the health care system. It is time to put an end to human gene patents.

Myriad's patent claims over isolated DNA and cDNA should be invalidated. If gene discoverers want to expand the scope of patentable subject matter under Section 101, their remedy lies with Congress, not the courts.

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AMICUS
CURIAE
BRIEF

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENERICS, INC., *et al.*,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF *AMICI CURIAE* ANIMAL HEALTH INSTITUTE AND MERIAL LIMITED IN SUPPORT OF RESPONDENTS

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INTERESTS OF *AMICI CURIAE*[1]

Amicus Curiae Animal Health Institute ("AHI") is a trade association representing companies in the animal health field. AHI is made up of 23 member companies[2] who supply farmers, veterinarians, and pet owners with a comprehensive range of pharmaceuticals, vaccines, and diagnostics developed and produced using both traditional technologies and modern biotechnology. The animal health industry has a multi-billion dollar impact on the U.S. economy annually, and its reach extends to much broader industries and concerns. Animal health inventions developed by AHI members—such as vaccines for cancer, foot and mouth disease, West Nile virus, avian flu, E. coli, and the H1N1 virus—not only improve the health, welfare, and productivity of animals, but also ensure food safety, protect human health, support a competitive and sustainable agricultural sector, and help to preserve the environment.

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[1] Pursuant to Supreme Court Rule 37.6, counsel for *Amici Curiae* represents that none of the parties or their counsel authored this brief in whole or in part and that no person or entity other than *Amici Curiae* made a monetary contribution to its preparation or submission. Petitioners have lodged a blanket consent to the filing of *amicus* briefs, and written consent by Respondents to the filing of this brief has been lodged with the Clerk of Court.

[2] The licensed and affiliate members of AHI are: Abbott Animal Health; Bayer Healthcare LLC, Animal Health Division; Bioniche Animal Health USA; Boehringer-Ingelheim Vetmedica, Inc.; Colorado Serum Company; ECO Animal Health; Elanco Animal Health; Merck Animal Health; Merial Limited; MVP Laboratories, Inc.; Novartis Animal Health US, Inc.; Phibro Animal Health; Virbac Corporation; Zoetis; AlcheraBio LLC; Benchmark Biolabs, Inc.; Animal Clinical Investigation; Aratana Therapeutics, Inc.; Biotechnical Services, Inc.; Mars Veterinary; MPI Research; Nestle Purina PetCare Company; and VetPharm, Inc.

AHI members annually invest hundreds of millions, if not billions, of dollars on the innovations, research, and science necessary for advances in pharmaceuticals, biologics, and pesticides for animals. Many of the products that AHI's members are developing stem from discoveries of creating isolated deoxyribonucleic acid ("DNA") molecules associated with animal disease, and AHI's members have applied for and received numerous patents for inventions involving isolated DNA molecules. Thus, they have a significant interest in the patentability of created DNA molecules.

Amicus Curiae Merial Limited ("Merial"), one of AHI's member companies, is a world-leading animal health company with its North American headquarters in Duluth, Georgia. Merial's world-wide 2010 sales were over $2.6 billion. Merial provides a comprehensive range of pharmaceutical products, vaccines, and diagnostic products to enhance the health, well-being, and performance of livestock, pets, and wildlife. Merial works with governments around the world to contain and manage various animal diseases for the benefit of both animals and humans.

Merial has a proven track record of discovering and developing cutting edge animal health products, and the company has launched new products every year since its inception in 1997. To that end, Merial makes significant investments in research and development. Merial develops and manufactures pharmaceuticals and vaccines with the highest level of quality, safety, and efficacy through a network of nine research and development centers and fifteen manufacturing sites. Merial employs approximately 5,700 people worldwide. More than half of Merial's research and development group is stationed in the United States, and Merial invests over $100 million annually in research and development in the United States alone.

Like other AHI members, Merial has applied for and received numerous patents for inventions involving isolated DNA molecules. Merial has a particular interest in the issues involved in this appeal because of a recent decision by the United States Court of Appeals for the Federal Circuit involving one of Merial's patents. *See Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282 (Fed. Cir. 2010). In the *Intervet* case, Judge Dyk, in an opinion concurring in part and dissenting in part, questioned whether one of the patent's claims covering an isolated DNA molecule constituted patentable subject matter under 35 U.S.C. § 101. *See Id.* at 1292 (Dyk, J., concurring in part and dissenting in part).

SUMMARY OF THE ARGUMENT

The question presented, "[a]re human genes patentable," is answered, generally speaking, in the negative. Genetic material, as it exists in the human body, does not constitute patentable subject matter. The question presented by petitioners was carefully crafted to evoke an emotional response—in particular, to frame the issue as one concerning whether the natural makeup of humans, *i.e.* their DNA, can be owned by someone else. Patents to human genes, however, are not the same as patents to isolated (*i.e.* created) DNA molecules. Thus, the more important, narrower question is whether isolated genetic molecules such as those covered by the challenged patent claims—which do not occur in nature, which are not found in the body of a human or animal, and which require substantial transformation from the genetic material indigenous to organisms—constitute patentable subject matter under 35 U.S.C. § 101. The answer to that more precise question is "yes."

When it comes to patent eligibility, a DNA molecule—although perhaps more complex—should be treated no differently than other molecules, for example polymers (*see, e.g.*, C.A. App. A3707 at ¶ 25). More than anything, this case is about chemicals and, in particular, whether a human-made molecule, which is not found in nature and which has markedly different characteristics from any substance found in nature, but which is derived from a larger, naturally occurring molecule, is eligible for patenting. Under the current patent system, as established by Congress, the answer, again, is "yes."

The consequences of ruling against the patentability of human-created genetic molecules are real and vast.[3] Such a decision would (i) undermine innovation and inhibit investment in all new genetic technologies, since the incentives provided by the patent system would no longer exist and (ii) likely create dissonance between the patent laws of the United States and those of the rest of the world.

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[3] Petitioner and other *Amici Curiae* that submitted briefs in support of the Petitioner suggest that this Court could craft a narrow ruling that impacts only isolated DNA molecules with respect to humans. There appears to be no legal basis for limiting a "narrow" order to the genetic materials of humans only (as opposed to, for example, the isolated genetic molecules of animals and other organisms), and therefore this Court's opinion will affect a broad swath of industries.

First, the patent laws of the United States are, of course, designed to reward innovators by giving them an exclusive right of limited duration in which to practice their invention(s). Petitioners' Brief focuses primarily on the misplaced notion that this system is somehow unjust, at the expense of fully addressing whether isolated molecules constitute patentable subject matter. It appears that Petitioners' main grievance is not that created genetic molecules purportedly constitute unpatentable subject matter, but instead that the United States' patent laws are working as intended with the result that Petitioners are excluded from practicing someone else's invention. Petitioners have it backwards. If the statutory incentives for invention with regard to created genetic molecules are eradicated, innovation in that field will cease or, at the very least, be substantially diminished. Thus, Petitioners would be left in the same position they are now, unable to practice an invention (since it would not exist), yet society as a whole would suffer since, again, the invention would not exist. This situation would carry forward, and new DNA-based inventions like the claimed isolated DNA molecules at issue would never be developed.

This same *quid pro quo* of patent law also applies to the animal health industry. The ability of AHI's members to bring DNA-based animal health products to market depends heavily on their ability to recoup the substantial investments necessary to discover, develop, obtain regulatory approval for, and commercialize inventions relating to human-created genetic material. To get back these investments, Merial and other AHI members rely on the ability to patent their created DNA molecule discoveries and on the limited period of exclusivity that comes with such patents. If created DNA molecules were not patentable, this important incentive would disappear.

Second, there are benefits to global patent law harmonization that would be undermined by a ruling that calls into question the validity of DNA-based inventions. In addition to the numerous patents involving isolated DNA molecules issued by the United States Patent and Trademark Office ("PTO") and upheld by the Federal Circuit, the European Patent Office ("EPO") allows for the patentability of biological material, such as DNA, provided the material is isolated from its natural environment or produced by means of a technical process. With respect to patents related to those at issue here, the EPO has praised European counterparts to the challenged patents for their innovation. In addition, a recent decision from the Federal Court of Australia held that a patent related to the ones at issue here, covering isolated genetic molecules, is patentable provided that the other requirements for patentability are met. Harmonization of what constitutes patentable subject matter is particularly important to global companies, like Merial, who usually patent related inventions in numerous countries.

Further, the PTO has approved thousands of patents involving isolated DNA molecules and, when these patents have been challenged, the Federal Circuit has upheld them. In so doing, the PTO and Federal Circuit have been correct as a matter of law because created DNA molecules (i) fit squarely within the definition of "manufacture[s]" and "compositions of matter," or at the very least "new and useful improvements thereof," and (ii) are chains of chemically joined nucleotides that, as courts have recognized, constitute complex chemicals with uses and properties beyond those that occur naturally. Created DNA molecules constitute patentable subject matter because they are products of processes requiring substantial human intervention, which result in chemically and structurally altered substances with properties and uses that are vastly different from anything found in nature (C.A. App. A3708 at ¶ 29).

Moreover, created DNA molecules do not fit into any of the judicially-created exceptions against patenting laws of nature, physical phenomena, or abstract ideas since, unlike the areas those exceptions cover, isolated DNA molecules are substances created only as a result of human intervention and effort. Indeed, in order to create an isolated DNA molecule, a human must first use ingenuity to identify and define that molecule and then apply advanced technology to either chemically isolate that molecule from the host of surrounding genetic material in the body or synthesize that molecule (*see, e.g.*, C.A. App. A3708; A4320-22; A4770-72).

It is of no moment that created DNA molecules are themselves derived from other naturally occurring substances because they, like all chemical inventions, remain uniquely created substances that are the result of assembling materials found in nature. *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1293 (2012). Thus, patenting isolated DNA molecules does not run afoul of the purpose of these exceptions, which is to ensure that abstract concepts and qualities, rather than human engineered substances, remain free for all to use.

With regard to *Amici Curiae*, a broad ruling on the question before this Court may have sweeping ramifications with respect to the patentability of inventions derived from genetic materials of animals, plants, and viruses. For example, AHI's members, such as Merial, are focused on developing novel products for treating and preventing the diseases that affect the global animal population, which include products to protect the health of (i) production animals such as cows, poultry, swine, and sheep; (ii) pets such as dogs and cats; and (iii) wildlife. The work of AHI's members helps not only animals, but also serves to protect the health of the human population, sustain agriculture, and preserve the environment.

ARGUMENT

I. Public Policy Strongly Favors a Holding that Created DNA Molecules Constitute Patentable Subject Matter Under 35 U.S.C. § 101.

A. Ruling that created DNA molecules are not patentable would have a substantial adverse impact on innovation, including the investment-backed expectations of the animal health industry.

The United States patent system is founded on the principle that a limited right to exclude is the proper incentive and exchange for the publication of an invention. As succinctly put by Abraham Lincoln:

> Next came the patent laws. These began in England in 1624, and in this country with the adoption of our Constitution. Before then any

> man [might] instantly use what another man had invented, so that the inventor had no special advantage from his own invention. The patent system changed this, secured to the inventor for a limited time exclusive use of his inventions, and thereby added the fuel of interest to the fire of genius in the discovery and production of new and useful things.

Abraham Lincoln, Lecture 'Discoveries, Inventions and Improvements' (22 Feb 1860), in 5 Complete Works of Abraham Lincoln 113 (John George Nicolay and John Hay eds., 1894). Without this critical right to exclude, our 16th President recognized that innovators would be unable to protect their investment in inventions and thus would wither the progress of science and useful arts.

Merial and AHI's other members can afford to bring new animal health inventions to the public only if they can recoup the substantial upfront investments necessary to (i) discover, research, and develop inventions; (ii) conduct clinical trials and obtain regulatory approval for them; and (iii) market them to the public. Our patent system—as well as the systems in nearly every other developed nation—is designed to ensure that these substantial investments are recovered by granting patent protection for inventions to those that discover and develop new technologies for a limited period of time. Excluded from the marketplace are those who would reap the fruits of the research and development labor without having risked the initial investment.

It is important to consider that patents to created DNA molecules do not prevent humans from using their genes in any of the ways that their genes have been used since the dawn of time. For example, the challenged patents do not rob humankind of a right or ability of which they were previously privy, such as transcribing DNA into mRNA within a human body.[4] To the contrary, patents to created DNA molecules merely protect uses of isolated DNA molecules, once removed from the natural environment, so that those isolated molecules can be put to useful purposes that did not previously exist.[5] The purpose of the patent system is to reward those inventions by providing innovators with a protective right to exclude.

This protection is the essence of patents. *See* U.S. Const. art. I, § 8, cl. 8; *see also Rite-Hite Corp. v. Kelley Co.*, 56 F.3d 1538, 1563 (Fed. Cir. 1995) ("Exclusivity in commercialization enables a patentee to recoup its investment in research, production, and marketing a new product."). This period of exclusivity is particularly important to the animal health industry because profit margins for most animal health products are relatively small, especially when compared to those in the human pharmaceutical industry. The ability of AHI member companies, such as Merial, to discover and obtain patent protection on created DNA molecules has been of enormous benefit to both animals and humans. The limited period of exclusivity afforded by patents on such molecules has permitted AHI's members to make the substantial investments necessary to develop and bring to market a number of DNA-based products for the treatment and/or prevention of significant diseases affecting the global animal population.

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[4] Although preemption was a concern in *Mayo*, that is not a concern here. The challenged patents concern specific isolated DNA molecules and do not preempt people from using human genes or the information contained in human genes.

[5] To be patentable, isolated DNA molecules must also meet the utility requirement of § 101.

For example, animal health products that have been developed, or are in the process of being developed, based on inventions involving created DNA molecules include a treatment for mammals who are suffering from acute or chronic renal failure and vaccines against numerous infectious animal diseases. Such DNA-based vaccines include those against West Nile virus, which infects birds, horses, dogs and cats, is widespread in Africa, and is known to infect and cause a seasonal epidemic in humans in North America; porcine reproductive and respiratory syndrome (PRRS) virus, which causes a disease in pigs that results in reproductive failure in pregnant sows and respiratory failure in neonatal pigs; infectious bursal disease virus, which causes a highly contagious disease of young chickens; equine herpesvirus, which can cause respiratory disease in horses; and feline caliciviruses, which is a principal source of upper respiratory tract conditions in cats. Created DNA molecules have significant utility; for instance they may function as probes and primers that allow scientists to determine the susceptibility of a subject to particular genetic disorders or, additionally, may serve as the fundamental building block in live vector vaccines (*see, e.g.*, C.A. App. A3813; A3840-41; A4322-23; A4728-29; A6771).

In addition to their own discoveries, AHI companies, including Merial, have entered into research collaborations with universities to discover and develop DNA-based inventions or have licensed from universities DNA-based inventions that have already been discovered and patented by university scientists. Because universities may lack the resources necessary to bring products to market, they often license their discoveries to companies like Merial for development. These patent licensing arrangements provide the universities with much needed revenue streams while providing commercial entities with access to DNA-based inventions. These arrangements also benefit the public since they often result in the development of novel products for the treatment and prevention of serious diseases affecting the global animal population.

For example, Merial introduced the world's first vaccine aimed at preventing a devastating disease impacting the pork industry, Postweaning Multisystemic Wasting Syndrome ("PMWS"). Merial's vaccine was based on the pioneering work of scientists at Merial in collaboration with two universities, who were able to discover, isolate, and characterize DNA from a previously unknown type of virus that is responsible for PMWS. In developing such inventions, AHI member companies, including Merial, expect that they will receive a limited period of exclusivity flowing from the patents on their inventions. Without that expectation, AHI member companies could not justify the enormous upfront investments necessary to develop and commercialize these isolated DNA-based inventions. The AHI member companies' expectations of patent protection have been soundly justified by the practice of the PTO and the law of the Federal Circuit.

The PTO has granted patents directed to isolated DNA molecules for over 25 years (C.A. App. A3467 (n.11); A3710 at ¶ 35). The PTO's 2001 Utility Examination Guidelines themselves show that over the prior 10 years, the PTO had issued at least 2,645 patents with claims to "isolated DNA" (C.A. App. A3467; A3710). Moreover, the Guidelines make clear that "[a] purified DNA *molecule* isolated from its natural environment . . . is a chemical compound and is patentable if all the statutory requirements are met." (C.A. App. A3973; *see also* A3971-72; 66 Fed. Reg. 1092, 1094 (Jan. 5, 2001) (emphasis in original)). In other words, the PTO has made clear its own policy of granting patent protection for inventions involving isolated DNA molecules. Moreover, when these patents have faced challenges, the Federal Circuit has upheld them. *See, e.g., In re Deuel*, 51 F.3d 1552, 1555, 1560 (Fed. Cir. 1995) (reversing rejection of claims directed to a "purified and isolated DNA sequence"); *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991) (affirming patentability of claims directed to, inter alia, a "purified and isolated DNA sequence"); *cf. In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009) (affirming obviousness determination of claim to DNA encoding a natural protein, without questioning that claim constituted patentable subject matter); *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993) (affirming award of priority of invention for a claim directed to a DNA molecule). AHI member companies have thus relied on the policies of the PTO and the holdings of the Federal Circuit to continue the research and development of, and to obtain patent protection on, the DNA-based inventions that benefit animals and humans worldwide.

Standing against this history of patent protection, the district court's ruling here threatens to disrupt severely the investment-backed expectations AHI members and other entities that rely on patent protection to justify the expense of developing DNA-based inventions. If that ruling were to stand, Merial and other AHI member companies would be forced to consider the significant risk that, because DNA-based inventions would not be patentable, any meaningful investment in the development of those inventions might not be recoverable. In many instances, the district court's ruling would force AHI member companies to forgo any research into or the development of new DNA-based animal health products because the enormous upfront investment could not be justified.

B. Ruling that created DNA molecules are not patentable would create dissonance between the patent laws of the United States and those of the rest of the world.

Commentators and legislators alike have long recognized the benefits of global patent law harmonization. Over the past several decades, the United States has made several attempts to harmonize its patent law with global patent law, including the Paris Convention, the Patent Cooperation Treaty, and the Trade-Related Aspects of Intellectual Property Rights. Just two years ago, then Under Secretary of Commerce and Director of the PTO, David Kappos, made a call for this global harmonization: "I urge us all to begin the process of patent law harmonization anew, now. I urge us all to search for common ground. I urge us all to let best global policy and best practices be our guide." David Kappos, *A Global Call for Harmonization*, USPTO.GOV (April 5, 2011), *available at* http://www.uspto.gov/news/speeches/2011/kappos_london.jsp.

Less than six months later, Congress passed the Leahy-Smith America Invents Act ("AIA"), which represents the latest, and the most significant, step toward global patent harmonization. The AIA implemented the recommendations of the National Academies of Science, which called for greater harmonization of domestic patent laws with those of other nations and implements several measures that bring United States' patent law closer to those of European and other nations. *See* S. Merrill, R. Levin & M. Myers, "A Patent System for the 21st Century" (2004).

Ruling against the patentability of created genetic molecules would set back the recent strides that have been made toward global patent harmonization, because many of the United States' largest trade partners allow for the patenting of created genetic molecules. For instance, in 1999, the European Patent Council incorporated provisions that allow for the patentability of biological material, such as DNA, if the material is isolated from its natural environment or produced by means of a technical process (*see* OFFICIAL JOURNAL OF THE EPO, Dec. of the Admin. Council of 16 June 1999 amending the Implementing Regulations to the European Patent Convention, *available at* http://archive.epo.org/epo/pubs/oj99/7_99/7_4379.pdf). Following the adoption of these provisions, the EPO, the administrative body that is responsible for granting European patents, has continued to issue patents on isolated genetic molecules, including those related to the patents before this Court (*see* European Patent Nos. 699,754; 705,903; 705,902; 785,216). Myriad was also granted related patents in Canada (*see* Canadian Patent Nos. 2,196,797; 2,196,790, and 2, 196,795), Australia (Australian Patent Nos. 686,004; 691,958), New Zealand (New Zealand Patent No. 326,525), and Japan.

Not only have international patent offices granted patents claiming isolated DNA molecules, the Federal Court of Australia recently upheld the patentability of Myriad's Australian patent which corresponds to the patent at issue before this Court *Cancer Voices Austl. v. Myriad Genetics Inc.*, FCA 65 (15 Feb. 2013), *available at* http://www.austlii.edu.au/au/cases/cth/FCA/2013/65.html. There, the Court found that isolated genetic material is patentable under Australian law. In so holding, the Australian Court remarked:

> It would lead to very odd results if a person whose skill and effort culminated in the isolation of a micro-organism (*a fortiori*, an isolated DNA sequence) could not be independently rewarded by the grant of a patent because the isolated micro-organism, no matter how practically useful or economically significant, was held to be inherently non-patentable.

Id. at ¶ 109.

Similarly, here, it would lead to "very odd results" if the United States' patent laws refuse to recognize the patentability of created genetic molecules, despite the consensus that has developed among some of the United States' largest trading partners that such created DNA molecules are patentable. For global innovators, such as Merial, with a number of closely related patents in numerous countries that are directed to particular inventions, it is critical for there to be uniformity between the United States' patent laws and those of other developed nations. Moreover, if the United States does not protect innovation in advanced technological fields such as biochemistry, that technology will move overseas and this country will, as an inevitable result, suffer a global competitive disadvantage.

II. Created DNA Molecules Are Patentable Subject Matter under 35 U.S.C. § 101.

Above all, AHI's members justifiably rely on patent protection for isolated (*i.e.*, created) DNA-based inventions because it is correct as a matter of law. Section 101 provides: "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor[e] . . . ." 35 U.S.C. § 101. The Federal Circuit has characterized this Court's decisions as having "consistently construed § 101 broadly, explaining that '[i]n choosing such expansive terms . . . modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope.'" *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 689 F.3d 1303 (Fed. Cir. 2013) (quoting *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010)). Applying this statutory framework, created nucleic acid molecules are patentable subject matter whether viewed as compositions of matter, manufactures, or any useful improvement thereof.

A. Created DNA molecules are compositions of matter or new and useful improvements thereof under § 101.

As the Federal Circuit correctly recognized, claims to created DNA molecules qualify as "compositions of matter" or "new and useful improvement[s] thereof" under § 101. *Ass'n for Molecular Pathology*, 689 F.3d at

1324-25. This Court has held that compositions of matter cover "all compositions of two or more substances and [includes] all composite articles, [including the] results of chemical union . . . ." *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980).

Isolated DNA molecules are a chain of organic compounds composed of nucleotides linked to a phosphate group (*see, e.g.*, C.A. App. A4290; A4313; A4317-19; A4322-25). These chemical entities therefore constitute compositions of matter under the *Chakrabarty* definition. Both the Federal Circuit and the PTO have correctly recognized that isolated DNA molecules are complex *chemicals.*[6] *See, e.g., Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d at 1206; *see also* PTO's 2001 Utility Examination Guidelines, 66 Fed. Reg. at 1093 (C.A. App. A3972) ("Like other chemical compounds, DNA molecules are eligible for patents when isolated from their natural state . . . ."). Thus, with respect to patent eligibility, created DNA molecules should be treated no differently than other human-made molecules that are derived from larger, naturally occurring, molecules.

Created DNA molecules are not identical to DNA as it exists in nature and thus, like other patent eligible human-made molecules, possess new forms, qualities, and properties that are not found in nature (C.A. App. A3707-08; A3709-10; A4322-24; A4412; A4413; A4414-15; A4418; A4424-25; 4728-29). *See also Ass'n for Molecular Pathology*, 689 F.3d at 1325 ("The isolated DNA molecules before us are not found in nature."). Specifically, human DNA in its natural state is organized into chromosomes and comprises a long strand of millions of nucleotides (*see, e.g.*, C.A. App. A4320-22). This long strand forms a tightly coiled bundle with DNA binding proteins called histones. A particular DNA molecule within the chromosome is not identifiable or useful in its native form (*see* C.A. App. A3707-08; A4320-25). In contrast, the claimed nucleic acid molecules have a defined beginning and end, and exist independently of the DNA binding proteins and the additional millions of nucleotides of the chromosome (*see id.*). Further, in order to create an isolated DNA molecule, humans must first apply creativity to subjectively identify and define that molecule and then, using advanced technology, chemically excise that molecule from the surrounding genetic material (thus creating a new molecule that is not found in nature) (*see, e.g.*, C.A. App. A3708; A4320-22; A4770-72).

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[6] At their most basic level, isolated DNA molecules are compositions of individual chemical elements, namely carbon, hydrogen, oxygen, nitrogen, and phosphorous (C.A. App. A4317).

Thus, by the same reasoning advanced in *Chakrabarty*—that patentable subject matter had "markedly different characteristics from any [substance] found in nature," 447 U.S. at 310—the challenged claims[7] are patent eligible. In particular, as the Federal Circuit correctly recognized, "Although isolated DNA is removed from its native cellular and chromosomal environment, it has also been manipulated chemically so as to produce a molecule that is markedly different from that which exists in the body." *Ass'n for Molecular Pathology*, 689 F.3d at 1328. Accordingly, as complex chemicals composed of chemically joined nucleotides, created DNA molecules are patentable as new and useful compositions of matter, or at the very least as "new and useful improvements thereof," within the meaning of § 101.

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[7] The challenged claims include Claims 1, 2, and 5 of United States Patent No. 5,747,282 ("the '282 Patent"), in addition to the claims identified by Petitioners at Pet. App. 426-28a.

B. Created DNA molecules are manufactures under § 101.

Even if created DNA molecules somehow did not fit within the definition of "compositions of matter" or "new and useful improvements thereof" (as they should), they qualify as "manufactures" under § 101. In particular, isolated DNA molecules are products of processes that result in chemically- and structurally-altered substances with vastly different properties and uses from the natural starting material. These are precisely the qualities of a "manufacture" as interpreted by the courts. *See Chakrabarty*, 447 U.S. at 308 (citing *Am. Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1, 11 (1931)).

The claims are drawn to a particular chemical entity, not just to a DNA molecule. To find and create a particular isolated DNA molecule involves a significant degree of human manipulation and intervention because an inventor must, *inter alia*, (i) choose whether an isolated DNA molecule will be single or double stranded; (ii) define the length, complexity, and nucleotide composition of that molecule; and (iii) choose whether that molecule will be used as a primer (and thus will be designed to have a sequence that is the reverse complement of a region of target DNA and that has a particular melting temperature) (*see* C.A. App. A3707-08; A3878; A4324; A4341-4343). The resulting isolated DNA molecule is stripped of its chromosomal environment, released of the strictures of the regulation of the cell, devoid of its native tertiary structure, and thus no longer serves the same function as it did in the human body. In short, the form and function of created DNA molecules is markedly different from DNA as it exists in the body.

Finding in § 101's language a clear indication that "Congress plainly contemplated that the patent laws would be given wide scope," this Court has adopted a "broad construction" of the term "manufacture." *Chakrabarty*, 447 U.S. at 308. Consistent with its dictionary definition, this Court has held that "manufacture" encompasses any "production of articles for use from raw or prepared materials by giving to these materials new forms, qualities, properties, or combinations, whether by hand-labor or by machinery." *Id.* (citation and punctuation omitted).

Created DNA molecules are "manufacture[s]" under this definition since an "isolated DNA molecule" necessarily involves human intervention. The term "isolated" used in the context of a patent claim directed to an "isolated DNA molecule" ties the claimed invention to the production of a new and useful article, made through human intervention and innovation, that is different from anything found in nature (C.A. App. A4291; A4320-24; A4335; A4336-39). This is because created DNA molecules do not exist in nature, but rather are only created by human innovation in the laboratory (C.A. App. A4291; A4320-24; A4335; A4336; A4338-39).

The challenged patents teach that created DNA molecules must be either (i) chemically synthesized or (ii) chemically excised from the other sequences in the genome and from any proteins or other cellular components, that naturally accompany the particular DNA sequence of interest (*see, e.g.*, '282 Patent, col. 19:8-18 (JA 859); *see also* C.A. App. A4291 ("[S]omeone of ordinary skill in the art would understand that 'isolated DNA' has been extracted from the cell and excised from the chromosome, or chemically synthesized.")). Accordingly, created DNA molecules are the product of human manufacturing.

Further, the manufacturing processes for creating isolated DNA molecules require substantial human involvement. Creating isolated DNA molecules, whether via chemical synthesis or excision, requires several involved and highly technical steps (*see, e.g.*, C.A. App. A3708; A4291; A4320-22; A4336; A4341-42; A4770-72). In fact, the creation of isolated DNA molecules relies on molecular-scale machinery such as restriction endonucleases, DNA polymerases, DNA ligase, reverse transcriptase, and other enzymes, that chemically alter DNA (*see, e.g.*, C.A. App. A132-33; A595-97; A612-14; A2469; A4336; A4341-42).

These laboratory techniques used to create isolated DNA molecules all result in chemical and structural changes to any starting material (C.A. App. A3707-08; A4322; A4324; A4336-37; A4412; A4424-25). For example, the common polymerase chain reaction ("PCR") process results in isolated DNA molecules that are chemically and structurally different from the individual nucleotide building blocks or from any naturally occurring gene (C.A. App. A3707-08; A3709; A4336; A4424-25). Likewise, the creation of isolated DNA molecules via chemical excision from a cellular environment results in a product that is structurally different from chromosomal DNA in its natural environment (*see, e.g.*, C.A. App. A4321-22; A4324; A4338-39; A4424-25). Thus, the process of isolating DNA molecules gives "new forms" to the raw materials that existed at the start of the process. *Chakrabarty*, 447 U.S. at 308.

The resulting human-created DNA molecules also have new properties and uses that do not exist in nature (C.A. App. A4320-24, A4325, A4335- 39; A6769-71). For example, isolated DNA molecules can be cloned into expression vectors for purposes of creating vaccines against a particular disease (*see, e.g.*, U.S. Patent No. 6,368,601, col. 4:11-53). Isolated DNA molecules can also be used as probes in assays designed to diagnose a disease or as primers in PCR reactions (*see e.g., id.*, col. 5:14-23; C.A. App. A4322-23). Naturally-occurring genes simply cannot be used in these ways (C.A. App. A4323; A6769-71).

Any assertion that the creation of isolated DNA molecules is akin to mining a mineral in the earth or plucking a leaf from a tree is premised on misunderstandings of (i) the level of human intervention necessary to create isolated DNA molecules and (ii) the differences between isolated DNA molecules and anything found in nature. *See Intervet*, 617 F.3d at 1295 (Dyk, J., concurring in part and dissenting in part) ("It would be difficult to argue, for instance that one could patent the leaves of a plant merely because the leaves do not occur in nature in their isolated form."). Rather, because created DNA molecules only exist as a result of human intervention, and because their creation imparts new qualities, properties, and uses from any starting material found in nature, isolated DNA molecules are patentable as new manufactures under § 101.

III. Created DNA Molecules Are Not Excluded From Patent Protection Under Any of the Limited Judicially Created Exceptions.

Although § 101 is broad, *Amici Curiae* recognize that it is not unlimited. This Court has set forth only "three specific exceptions to § 101's broad patent-eligibility principles: 'laws of nature, physical phenomena, and abstract ideas.'" *Bilski*, 130 S. Ct. at 3225 (quoting *Chakrabarty*, 447 U.S. at 309). These specific exceptions were crafted to ensure that abstract "concepts" and qualities remain a "'part of the storehouse of knowledge of all men . . . free to all men and reserved exclusively to none.'" *Id.* (emphasis added) (quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U. S. 127, 130 (1948)). The Federal Circuit recognized these judicially created exceptions and correctly determined they were inapplicable to whether the challenged claims constituted patentable subject matter under § 101. *See Ass'n for Molecular Pathology*, 689 F.3d at 1234.

The Federal Circuit correctly held that isolated DNA molecules are not products of nature because, "[w]hile they are prepared from products of nature, so is every other composition of matter." *Ass'n for Molecular Pathology*, 689 F.3d at 1325. Neither this Court nor the Federal Circuit has held that "substances," such as isolated DNA molecules, should be excluded from the scope of § 101 simply because they are derived from "naturally occurring substances." These exceptions do not exclude from patent protection new and useful substances that are created only as a result of human intervention, even if those new and useful substances are derived from natural products. The *Funk Brothers* decision, for instance, does not prohibit the patenting of compositions derived from naturally occurring substances, but merely expresses this Court's concern regarding the patenting of abstract concepts such as "laws of nature" or "phenomena of nature." *See Funk Bros.*, 333 U.S. at 130.

As Justice Frankfurter explained in his concurring opinion in *Funk Brothers*, the problem with the patent claims at issue there was that rather than claiming particular mixtures of compatible bacterial strains—which would have been patentable, even though those strains are found in nature—the patentee attempted to claim all combinations of strains having the abstract and natural phenomenon of non-inhibition. *See Funk Bros.*, 333 U.S. at 133 (Frankfurter, J., concurring). As Justice Frankfurter wrote, "[i]nsofar as the court below concluded that the packaging of a particular mixture of compatible strains is an invention and as such patentable, I agree . . . ." *Id.* Justice Frankfurter stated that the patentee's combination of strains did not satisfy this description. Rather, "[t]he strains by which [the patentee] secured compatibility are not identified and are identifiable only by their compatibility." *Id.*

Thus, the *Funk Brothers* Court's concern was not that the patentee's claims were directed at natural substances *per se*, but rather that the patentee was attempting to claim the abstract, concept or principle of inhibition, which the Court considered to be "part of the storehouse of knowledge of all men." *Id.* at 130; *see also id.* at 132 (holding "the discovery of the natural principle itself" is not invention). Gravity, for example, constitutes one of these abstract principles of nature that is part of the storehouse of knowledge. This Court suggested that products derived from nature, as opposed to abstract principles, are patentable if as a result of the patentee's efforts they "acquire[] a different use" or an "enlargement of the range of their utility," or there is an "improve[ment] in any way [in] their natural functioning." *Id.* at 131.

This Court's subsequent decision in *Chakrabarty* confirmed that new compositions of matter may be patentable, even if they are derived from natural substances. Specifically, the *Chakrabarty* Court upheld the patentability of claims directed to a genetically engineered bacteria because the claims were not directed to a "natural phenomenon" but to "a product of human ingenuity having a distinctive name, character [and] use." *Chakrabarty*, 447 U.S. at 309-10 (citation and punctuation omitted). Claims to isolated DNA molecules do not give rise to the concerns that were at issue in *Funk Brothers*. Such claims are not claims to abstract "concepts," "principles," or "knowledge," but rather are directed to tangible chemicals, *i.e.* molecules, which as a result of human intervention have acquired different properties and uses from anything that exists in nature.

Moreover, the use of any information conveyed by the sequence of any isolated DNA molecules is not prohibited by virtue of any patent protection on the isolated DNA molecule itself. Scientists and others may use the sequence information conveyed by patented isolated DNA molecules in a variety of ways without infringing the patents, as is evidenced by the thousands of scientific papers published on the BRCA DNA sequences (*see, e.g.*, C.A. App. A3643-44; A5570-71). Because patents to isolated DNA molecules are not within any of the three specific exceptions to § 101's broad patent-eligibility principles and more generally do not in any way restrict the "storehouse of knowledge available to all men," created DNA molecules constitute patentable subject matter under § 101.

IV. This Court Should Not Give Credence to Petitioners' Complaints About the Patent System.

In its opinion, the Federal Circuit correctly dismissed several of Petitioners' attempts to override logic with emotional pleas:

> [I]t is important to state what this appeal is not about. It is not about whether individuals suspected of having an increased risk of developing breast cancer are entitled to a second opinion. Nor is it about whether the University of Utah, the owner of the instant patents, or Myriad, the exclusive licensee, has acted improperly in its licensing or enforcement policies with respect to the patents. The question is also not whether i[t] i[s] desirable for one company to hold a patent or license covering a test that may save people's lives, or for other companies to be excluded from the market encompassed by such a patent—that is the basic right provided by a patent, *i.e.*, to exclude others from practicing the patented subject matter. . . . Those questions are not before us. It is solely whether the claims to isolated BRCA DNA . . . meet the threshold test for patent-eligible subject matter under 35 U.S.C. § 101 in light of various Supreme Court holdings, particularly including *Mayo*.

* * *

> We would further note, in the context of discussing what this case is not about, that patents on life-saving material and processes, involving large amounts of risky investment, would seem to be precisely the types of subject matter that should be subject to the incentives of exclusive rights. But disapproving of patents on medical methods and novel biological molecules are policy questions best left to Congress, and other general questions relating to patentability and use of patents are issues not before us.

Ass'n for Molecular Pathology, 689 F.3d at 1324-25.

Petitioners seek to reframe the issue before the Court to be whether human genes can be patentable. That is a red herring. The challenged patents do not attempt to patent human genes. As set forth above, this case concerns only whether an isolated molecule—which is not found in nature, which possesses characteristics markedly different from those found in nature, and which can be put to a new use that was not previously known—is eligible for patenting. As the Federal Circuit correctly held, that should, in fact, be the case.

CONCLUSION

For at least the foregoing reasons, this Court should affirm the decision of the Federal Circuit that reversed the district court's decision in this matter and confirm that claims to novel created DNA molecules can constitute patentable subject matter under § 101.

Respectfully submitted,

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March 13, 2013

AMICUS
CURIAE
BRIEF

Supreme Court, U.S.
FILED
MAR 14 2013
OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, *ET AL.*,
Petitioners,

v.

MYRIAD GENETICS, INC., *ET AL.*,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF THE ASSOCIATION OF AMERICAN PHYSICIANS & SURGEONS, JANIS CHESTER, M.D., AND GRAHAM L. SPRUIELL, M.D., AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

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1. Does the Court exceed its Article III powers by answering the Petitioners' Question Presented instead of limiting the Section 101 analysis to the Patent Claims, as issued?

2. Does the creation of a judicial exception to Section 101 of Title 35 violate the Bicameral and Presentment Clauses as well as the Patent Clause?

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AUTHORITY

Robert L. Harmon, Cynthia A. Homan, and Charles M. McMahon, PATENTS AND THE FEDERAL CIRCUIT (10th Ed. 2011) 23, 24

No. 12-398

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Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

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INTERESTS OF *AMICI CURIAE*[1]

Amicus Association of American Physicians & Surgeons, Inc. ("AAPS"), is a national nonprofit association of thousands of physicians. Founded in 1943, AAPS has been a litigant in this Court and in other appellate courts. *See, e.g.*, *Cheney v. United States Dist. Court*, 542 U.S. 367, 374 (2004) (citing

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[1] This brief is filed with the blanket written consent of the Petitioners, and the filed written consent of Respondents. Pursuant to Supreme Court Rule 37.6, counsel for *Amici Curiae* authored this brief in whole, and no counsel for a party authored this brief in whole or in part, nor did any person or entity, other than *Amici* or *Amici's* counsel make a monetary contribution to the preparation or submission of this brief.

Association of American Physicians & Surgeons v. Clinton, 997 F.2d 898 (D.C. Cir. 1993)); *Association of American Physicians & Surgeons v. Mathews*, 423 U.S. 975 (1975). In addition, this Court has expressly made use of *amicus* briefs submitted by AAPS in high profile cases. *See, e.g., Stenberg v. Carhart*, 530 U.S. 914, 933 (2000); *id.* at 959, 963 (Kennedy, J., dissenting); *District of Columbia v. Heller*, 554 U.S. 570, 704 (2008) (Breyer, J., dissenting).

Amicus Janis Chester, M.D., privately practices psychiatry in Delaware, serves as chair of the Department of Psychiatry at a community hospital, is a member of the faculty at Jefferson Medical College and has held a variety of positions with organized medicine and psychiatry, locally and nationally.

Amicus Graham Lindley Spruiell, M.D., is in private practice in Massachusetts and specializes in forensic psychiatry and psychoanalysis.

The motto of AAPS is "*omnia pro aegroto,*" which means "all for the patient." The individual physician *Amici*, Drs. Chester and Spruiell, are likewise devoted to the best interests of their patients. Advancing patients' interests means supporting and defending incentives for medical innovations. *Amici* oppose categorical judicial exclusion of certain medical inventions from patentability because that will reduce incentives for these innovations, and result in fewer advances for patients.

As physicians and a physician's organization, *Amici* have a strong interest in defending full patentability for medical innovations so that inventions will improve the care of patients by physicians.

PRELIMINARY STATEMENT

Petitioners have asked the Court to resolve an abstract legal question, the question of whether a human gene is patentable subject matter under 35 U.S.C. § 101.[2] That gives the Court a Hobson's choice: either to issue a non-justiciable advisory opinion or to exercise legislative power by creating a judicial exception to 35 U.S.C. § 101 in violation of the Bicameral, Presentment and Patent Clauses of the Constitution of the United States. U.S. CONST. art. I, §1, U.S. CONST. art. I, §7, cl. 2, and U.S. CONST. art. I, §8, cl. 8, respectively.

To prevent such a dilemma, *Amici* suggest that the Court narrow its focus to the claims contained in the issued patents, *i.e.* to determine whether Claims 1, 2, 5, 6, and 7 of U.S. Pat. No. 5,747,282 ["('282 Patent)"], Claims 1, 6, and 7 of U.S. Pat. No. 5,837,492 ["('492 Patent)"], and Claim 1 of U.S. Pat. No. 5,693,473 ["('473 Patent)"] (cumulatively, "Respondents' Claims") contain patentable subject matter under Section 101. Respondents' Claims refer to "isolated DNA". They do not refer to: "native DNA"; "human DNA"; or the "human gene." By narrowing its focus to the claims as issued, the Court reaffirms its constitutionally assigned role: to resolve an actual case or controversy.[3]

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[2] In this brief, the word "Section" refers to a section of Title 35 unless the brief specifies otherwise.

[3] By staying within its constitutionally prescribed role, the Court avoids becoming embroiled in questions that are political, ethical, moral or metaphysical. It thereby avoids becoming a policy-maker.

Amici curiae strongly disagree with the Petitioners' major premise that the existence of Respondents' Patents thwarts innovation and research in the field of breast or ovarian cancer genetics. Petitioners' Brief at 2-4, 7-9, 24-25, 41-48, and 56-57. The converse is true. Rather, innovation has been promoted by the public disclosure of Respondents' patents. Respondents' Brief at 10. In fact, more than two dozen patents have been issued which have referenced the Respondents' '473 Patent (19 references),[4] the '282 Patent (9 references),[5] and the '492 Patent (3 references).[6] The referencing patents have been assigned to a variety of universities and medical schools, several commercial entities, and even the government of the United States. The fact that only two of the referencing patents are assigned to Myriad further establishes that Myriad's patents have not thwarted research and development in the field but actually have promoted such research and development.

SUMMARY OF THE ARGUMENT

This case is about the allocation of powers between and among the branches. It is not about what the law "ought to be."

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[4] *See* U.S. Pat. Nos. 7,897,356; 7,897,335; 7,534,565; 6,897,018; 6,875,592; 6,838,256; 6,686,163; 6,653,126; 6,596,481; 6,566,070; 6,492,109; 6,403,303; 6,344,320; 6,342,483; 6,306,628; 6,235,263; 6,030,832; 5,912,127; and 5,750,400.

[5] *See* U.S. Pat. Nos. 8,372,580; 8,110,185; 7,897,356; 7,781,199; 6,838,256; 6,686,163; 6,492,109; 6,342,483; and 6,258,536.

[6] *See* U.S. Pat. Nos. 8,076,065; 7,933,722; and 7,897,356.

The Separation of Powers Doctrine, as implemented by the language and structure of the Constitution, prevents the Judiciary from creating a judicial exception to Section 101, the legislated determination of patentable subject matter. The Patent Clause squarely places that responsibility in the hands of Congress. U.S. CONST. art. I, §8, cl. 8. The courts may not expand or contract what Congress says is patentable. Thus, a judicially created exception to the legislated definition of patentable subject matter is outside the scope of the Patent Clause and ignores the Presentment and Bicameral Clauses. Although the Executive Branch is similarly prevented from amending what Congress has legislated to be patentable subject matter, the Executive Branch, in its *amicus* brief, has abandoned its prior position that isolated DNA sequences are patentable. Such a complete reversal of position by the Executive Branch, without a change in the underlying authorizing legislation, is inconsistent with the Constitution because it creates a dispensing power in the Executive Branch.

Furthermore, this case is not justiciable. The scope of the subject matter to be considered by the Petitioners' "Question Presented" (*i.e.* Are human genes patentable?) is substantially beyond that contained in Respondents' Claims. The Respondents' Claims are for specified isolated DNA sequences. They are not for any human gene. In our claims-based patent system, an inventor's right to exclusivity extends no further than the claims granted. Consequently, this Court lacks and the courts below lacked the jurisdiction to determine whether a human gene is patentable. Courts may only determine if the claims, as granted, contain patentable subject matter. In order for the Court to respond to the hypothetical question of whether a "human gene" is patentable subject matter, the Court would have to render an advisory opinion in violation of the Constitution.

This Court may not strike down the Respondents' Claims by creating a judicial exception to Section 101. A judicially created exception to Section 101 overrides the considered judgments of both Congress and the President which had enacted Section 101 and invades their constitutionally assigned roles, to make and faithfully execute the laws, respectively.

The evidence that isolated DNA is patentable subject matter is strong. First, Congress and the President have enacted laws with the understanding that DNA sequences may be claimed as patentable subject matter. Second, the United States Patent and Trademark Office ("PTO") has issued rules and published examination procedures regarding the patenting of DNA sequences. Third, the PTO considers DNA sequences patentable subject matter since it has granted numerous patents for such claims. Fourth, various departments and agencies within the federal government are assignees of patents for isolated DNA sequences. Fifth, the United States Department of Health and Human Services ("HHS") is an assignee of the '282 patent.

The question of whether a human gene is patentable can only be answered by Congress. It is a legislative question.

ARGUMENT

I. CONGRESS HAS THE POWER UNDER THE PATENT CLAUSE TO DEFINE PATENTABLE SUBJECT MATTER, A POWER WHICH MAY NOT BE EXERCISED BY THE OTHER BRANCHES WITHOUT AMENDING THE CONSTITUTION.

A. The Power To Define Patentable Subject Matter Is Legislative.

The Patent Clause provides: "The Congress shall have Power ... To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries...." U.S. CONST. art. I, §8, cl. 8. From the beginning of our nation, Congress has exercised this power. Indeed, the first Congress provided for the issuance of "letters patent." *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 373 (1996) (referring to Act of Apr. 10, 1790, ch. 7, §1, 1 Stat. 109). Today, the patent statutes are codified in Title 35 of the United States Code.

B. Legislative Power May Only Be Exercised by Congress in Accord with the Bicameral and Presentment Clauses.

It is black-letter law that Congress, and only Congress, may enact a law in accord with "a single, finely wrought and exhaustively considered, procedure" as prescribed by the Bicameral and Presentment Clauses. *Immigration and Naturalization Service v. Chadha*, 462 U.S. 919, 951 (1983) ("*Chadha*"); *Clinton v. City of New York*, 524 U.S. 417, 439-440 (1998) ("*Clinton*"); *Metropolitan Washington Airports Authority v. Citizens for*

Abatement of Aircraft Noise, Inc., 501 U.S. 252, 276 (1991) ("*MWAA*").

The Bicameral Clause vests federal legislative power exclusively in a bicameral Congress. The Bicameral Clause provides: "All legislative Powers herein granted shall be vested in a Congress of the United States, which shall consist of a Senate and House of Representatives." U.S. CONST. art. I, §1.

The Presentment Clause, U.S. CONST. art. I, §7, cl. 2, sets forth the precise procedures by which Congress is permitted to make a law. The Presentment Clause provides:

> Every Bill which shall have passed the House of Representatives and the Senate, shall, before it becomes a law, be presented to the President of the United States; If he approve he shall sign it, but if not he shall return it, with his Objections to that House in which it shall have originated, who shall enter the Objections at large on their Journal, and proceed to reconsider it. If after such Reconsideration two thirds of that House shall agree to pass the Bill, it shall be sent, together with the Objections, to the other House, by which it shall likewise be reconsidered, and if approved by two thirds of that House, it shall become a Law...."

U.S. CONST. art. I, §7, cl. 2. These legislative steps are not empty formalities. Rather, they are commands which simultaneously require and limit the participation of the Senate, the House of Representatives, and the President in the lawmaking process. As such, they may be altered or evaded only by an Amendment to the Constitution. *See Clinton*, 524 U.S. at 449; *Chadha*, 462 U.S. at 958 n.23. In *Chadha*, this Court explained:

> Explicit and unambiguous provisions of the Constitution prescribe and define the respective functions of the Congress and of the Executive in the legislative process ... These provisions of Art. I are integral parts of the Constitutional design for the separation of powers ... "[T]he principle of separation of powers was not simply an abstract generalization in the minds of the Framers: it was woven into the document that they drafted in Philadelphia in the summer of 1787." *Buckley v. Valeo*, 424 U.S. at 124 .... [T]he Framers were acutely conscious that the bicameral requirement and the Presentment Clauses would serve essential constitutional functions .... It emerges clearly that the prescription for legislative action in Art. I, §§ 1, 7, represents the Framers' decision that the legislative power of the Federal Government be exercised in accord with a single, finely wrought and exhaustively considered, procedure.

Chadha, 462 U.S. at 945-951.

Executive power must faithfully execute the laws. *See* U.S. CONST. art. II, § 3. As this Court explained in *Youngstown Sheet & Tube Co. v. Sawyer*:

> In the framework of our Constitution, the President's power to see that the laws are faithfully executed refutes the idea that he is to be a lawmaker. The Constitution limits his functions in the lawmaking process to the

> recommending of laws he thinks wise and the vetoing of laws he thinks bad. And the Constitution is neither silent nor equivocal about who shall make laws which the President is to execute.

343 U.S. 579, 587 (1952).

Judicial power is likewise limited. Judicial power is limited to resolving an actual case or controversy. Courts do not resolve policy debates:[7]

> The constitutional role of the courts, however, is to decide concrete cases – not to serve as a convenient forum for policy debates. *See Valley Forge Christian College v. Americans United for Separation of Church and State, Inc.*, 454 U.S. 464, 472 (1982) ("[Standing] tends to assure that the legal questions presented to the court will be resolved, not in the rarified atmosphere of a debating society, but in a concrete factual context conducive to a realistic appreciation of the consequences of judicial action").

Massachusetts v. E.P.A., 549 U.S. 497, 547 (2007) (Roberts, C.J., dissenting).

Indeed, the Court below emphasized the point that courts should not address policy arguments.

> Under the statutory rubric of § 101, isolated DNA is a tangible, man-made composition of matter defined and distinguished by its objectively discernible chemical structure.

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[7] *Warner-Jenkinson Co., Inc. v. Hilton Davis Chemical Co.*, 520 U.S. 17, 28 (1997) ("The various policy arguments now made by both sides are thus best addressed to Congress, not this Court").

> Whether its unusual status as a chemical entity that conveys genetic information warrants singular treatment under the patent laws as the district court did is a policy question that we are not entitled to address. *Cf. Nat'l Fed'n of Indep. Bus. v. Sebelius*, 132 S.Ct. 2566, 2579 ... (2012) ("***[W]e possess neither the expertise nor the prerogative to make policy judgments. Those decisions are entrusted to our Nation's elected leaders, who can be thrown out of office if the people disagree with them.***"). Congress is presumed to have been aware of the issue, having enacted a comprehensive patent reform act during the pendency of this case, and it is ultimately for Congress if it wishes to overturn case law and the long practice of the PTO to determine that isolated DNA must be treated differently from other compositions of matter to account for its perceived special function. We therefore reject the district court's unwarranted categorical exclusion of isolated DNA molecules.

Association for Molecular Pathology v. Myriad Genetics, Inc., 689 F.3d 1303, 1330-31 (Fed. Cir. 2012) (Slip op. at 49-50) (emphasis added).

C. Legislative Power May Not Be Ceded to or Aggrandized by the Judicial Branch.

Our Constitution diffuses power in several ways. First, power is divided between the federal sovereign and the state sovereigns. Second, power is further diffused among the three branches of the federal government, *i.e.* the Legislative Branch, U.S. Const. art. I, the Executive Branch, U.S. Const. art. II, and the Judicial Branch, U.S. CONST. art. III.[8] The Bicameral Clause further diffuses federal legislative power by dividing Congress into two separate chambers, the Senate and the House of Representatives. U.S. CONST. art. I, §1.

The Court has repeatedly held "the lawmaking function belongs to Congress, U.S. CONST. art. I, § 1 and may not be conveyed to another branch or entity." *Loving v. United States*, 517 U.S. 748, 757 (1996) (internal citation omitted). Accordingly, "Congress manifestly is not permitted to abdicate, or to transfer to others the essential legislative functions with which it is ... vested." *Panama Refining Co. v. Ryan*, 293 U.S. 388, 421 (1935). "[I]t is a breach of the national fundamental law if Congress gives up its legislative power and transfers it to the President, or to the Judicial branch ...." *J.W. Hampton, Jr. & Co. v. United States*, 276 U.S. 394, 406 (1928); *see also Youngstown Sheet & Tube Co.*, 343 U.S. at 655 (Jackson, J., concurring) ("The Executive, except for recommendation and veto, has no legislative power"); *Field v. Clark*, 143 U.S. 649, 692 (1892) ("That Congress cannot delegate legislative power to the President is a principle universally recognized as vital to the integrity and maintenance of the system of government ordained by the Constitution").

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[8] *Muskrat v. United States*, 219 U.S. 346 (1911) ("That by the Constitution of the United States, the government thereof is divided into three distinct and independent branches, and that it is the duty of each to abstain from, and to oppose, encroachments on either").

Concerns of encroachment and aggrandizement of legislative power, as well as the abdication of legislative power by Congress, have been an integral part of this Court's separation of powers jurisprudence. *Mistretta v. United States*, 488 U.S. 361, 382 (1989) ("It is this concern of encroachment and aggrandizement that has animated our separation of powers jurisprudence and aroused our vigilance against the 'hydraulic pressure inherent within each of the separate Branches to exceed the outer limits of its power'").

The Separation of Powers Doctrine does not merely protect each branch from encroachments by the other two branches. Rather, the doctrine protects the people from the undue concentration of power in any branch. *MWAA*, 501 U.S. at 272 ("The structure of our Government as conceived by the Framers ... disperses the federal power among the three branches - ... placing both substantive and procedural limitations on each. *The ultimate purpose of this separation of powers is to protect the liberty and security of the governed*") (emphasis added).[9]

D. A Judicially Created Exception to Section 101 Impermissibly Exercises Legislative Power.

A judicially created exception to Section 101 is legislative in character and effect as it essentially amends Section 101. Amending legislation, as well as repeal of legislation, is a quintessentially legislative function requiring bicameral passage and presentment to the President.

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[9] In *Buckley v. Valeo*, the Court indicated the system of separated powers and checks and balances was regarded by the Framers "as a self-executing safeguard against the encroachment or aggrandizement of one branch at the expense of the other." 424 U.S. 1, 122 (1976).

Although not every Congressional action is subject to the bicameralism and presentment requirements, those requirements must be met when Congress exercises legislative power. Whether particular actions are an "exercise of legislative power depends not on their form but upon 'whether they contain matter which is properly to be regarded as legislative in its character and effect.'" *Chadha*, 462 U.S. at 952 (internal citation omitted).

The legislative character of an action may be established by an examination of the congressional action it supplants. This "Supplantation Principle" was used to analyze the constitutionality of the legislative veto in *Chadha*, 462 U.S. at 952 ("The legislative character of the one-House veto in these cases is confirmed by the character of the Congressional action it supplants"). The Court should extend this principle to apply to all non-Congressional exercises of legislative power including: "legislative actions" undertaken by departments and agencies within the Executive Branch, "legislative actions" undertaken by the Judicial Branch, and "legislative actions" undertaken by independent agencies.

In *Chadha*, the Court examined the constitutionality of the legislative veto found in section 244(c)(2) of the Immigration and Nationality Act of 1952. Public L. 82-414, 66 Stat. 163, 214 (1952). The Court found that §244(c)(2) had an essentially legislative purpose and effect. Despite acknowledging that §244(c)(2) authorized one house, by resolution, to require the Attorney General to deport an alien whose deportation would otherwise be canceled under §244, the Court reasoned that "the House took action that had the *purpose and effect of altering the legal rights, duties, and relations of persons*, including the Attorney General, Executive Branch Officials and Chadha, all outside the Legislative Branch." *Chadha,* 462 U.S. at 952 (emphasis added).[10] The Court explained that absent the House's action, Chadha would remain in the United States. Chadha's deportation could be accomplished only by new legislation requiring deportation, if at all. *Chadha,* 462 U.S. at 953-954.

Creating a judicial exception to section 101 is legislative in both character and effect. The relief sought – to create a judicial exception to section 101 – is the equivalent of legislation because it, in effect, amends Section 101. It affects the legal rights, duties and relations of many persons.

The power to "amend" an existing law is unquestionably a legislative power, which the Constitution vests solely in Congress. U.S. CONST. art. I, §1. *See Chadha*, 462 U.S. at 954 and *Clinton*, 524 U.S. at 438. It cannot be stressed too much that the Constitution begins with the allocation of legislative power solely to Congress. The first clause of the Constitution states: "All legislative Powers herein granted shall be vested in a Congress of the United States, which shall consist of a Senate and House of Representatives." U.S. CONST. art. I, §1.

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[10] *See also MWAA*, 501 U.S. at 276 ("In short, when Congress '[takes] action that ha[s] the purpose and effect of altering the legal rights, duties, and relations of persons ... outside the Legislative Branch,' it must take that action by the procedures authorized in the Constitution."). *See also id.* at 258 n.4.

Nothing is unclear or ambiguous about this language. "All" means "all".[11]

E. Considering *United States v. Symonds*, New Legislation Is Required for the Executive Branch To Reverse Course and Argue Isolated DNA Is Not Patentable Subject Matter.

1. Under *Symonds*, a federal agency may not issue an order or regulation that is inconsistent with the authorizing statute.

The principle that neither the Judiciary nor the President may unilaterally exercise legislative power applies equally to subordinate federal departments and independent agencies. Thus, the PTO may not issue regulations in conflict with Title 35, and the Department of Justice ("DOJ") may not advocate a position that is inconsistent with Title 35 and the regulations promulgated thereunder. The DOJ and PTO, like the President, must see that the laws are faithfully executed. Although the Court has generally allowed regulations as interstitial "lawmaking", *Wayman v. Southard*, 10 Wheat. (23

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[11] The "Plain Meaning Rule" is one of several canons of construction applied by courts to determine the meaning of statutory provisions. Courts typically turn to this canon before others. *Connecticut National Bank v. Germain*, 503 U.S. 249, 253-54 (1992) ("We have stated ... that courts must presume that a legislature says in a statute what it means and means in a statute what it says there ... When the words of a statute are unambiguous, then, this first canon is also the last: 'judicial inquiry is complete.'") (internal citations omitted). This canon should also be applicable to the interpretation of the Constitution, including its first word (*i.e.* the word "all").

U.S.) 1, 43 (1825) (Marshall, Ch. J.), it has struck down regulations which conflict with the authorizing statute. For example, in 1887, the Supreme Court struck down an order issued by the Secretary of the Navy that provided that a particular training vessel was not to be considered "at sea" in connection with the compensation of an officer for "sea service." The Court reasoned that the Secretary did not have the authority to declare something as "shore duty" that the statute requires the Navy to treat as "sea duty." The Court declared that the Secretary of the Navy only had authority to "establish regulations in execution of, or supplementary to, ***but not in conflict with***, the statutes defining his powers or conferring rights upon others." *United States v. Symonds*, 120 U.S. 46, 48-49 (1887) (emphasis added).

Furthermore, when an agency or executive department picks or chooses which laws or regulations to "faithfully execute." it turns rulemaking or executive action on its head – agency or executive department actions would control legislation instead of the rulemaking or executive actions being controlled by the legislation. Such a doctrine – agency or department control of legislation – has no support in the Constitution. It asserts a principle which would provide the executive departments, independent agencies and the President with an unlimited power – "a power to control the legislation of [C]ongress and paralyze the administration of justice." *Kendall v. United States ex rel. Stokes*, 12 Pet. (37 U.S.) 524, 613 (1838).

2. The PTO has issued regulations, guidelines and practices recognizing DNA sequences as patentable subject matter.

Subsections 1.821 through 1.825 of the patent rules recognize that nucleotide sequences are patentable subject matter. 37 C.F.R. §§ 1.821-1.825. *See also* Manual of Patent Examination Procedures ("MPEP") §2422. The PTO's favorable policy towards the patentability of isolated DNA was recognized below. An opinion concurring in part below said:

> For more than a decade the Patent Office's policy has been that "[a]n isolated and purified DNA molecule that has the same sequence as a naturally occurring gene is eligible for a patent because ... that DNA molecule does not occur in that isolated form in nature ...." 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001) ... The PTO concluded that isolated DNA is patentable because it is different from what is found in nature – the process of synthesizing it or isolating it changes it. While the PTO lacks substantive rule making authority, it is not without expertise in this area. The explicit statement of the Patent Office's position on isolated DNA, however, is simply a continuation of a longstanding and consistent policy of allowing patents for isolated natural products. *See id.* (noting U.S. Patent 141,072, claiming "[y]east, free from organic germs of disease," issued to Louis Pasteur in 1873); *cf. In re Bergstrom*, 427 F.2d 1394 (CCPA 1970) (isolated prostaglandins patentable).

> **According to the Patent Office, isolated DNA is no different from the isolated natural products of *Parke-Davis*. *See* 66 Fed. Reg. at 1093 (quoting Parke-Davis).**

Association for Molecular Pathology, 689 F.3d at 1343-44 (Moore, J., concurring) (slip op. at 14-15) (emphasis added). *See also* Resp. Brief at 3-5, 29-31, 37-38, and 49-50 (regarding the PTO's longstanding practice).

3. The PTO has recognized isolated DNA as patentable subject matter by issuing patents with claims for isolated DNA.

The PTO's recognition of the patentability of isolated DNA did not go unnoticed by the Federal Circuit. In his concurring opinion below, Judge Moore recognized the PTO's issuance of thousands of patents for isolated DNA. Considering *Symonds*, those patents could only have been issued if, and only if, isolated DNA is patentable subject matter. Judge Moore stated:

> Likewise, the United States Patent Office has allowed patents on isolated DNA sequences for decades, and, more generally, has allowed patents on purified natural products for centuries. There are now thousands of allowed patents with claims to isolated DNA, and some unknown (but certainly large) number of patents to purified natural products or fragments thereof...I believe we must be particularly wary of expanding the judicial exception to patentable subject matter where

> both settled expectations and extensive property rights are involved.

Association for Molecular Pathology, 689 F.3d at 1343 (Moore, J., concurring) (slip op. at 13-14) (footnotes omitted). *See also* Resp. Brief at 3, 30.

While it is apparent that this Court's decision could have a substantial economic impact upon the inventors of patents for isolated DNA as well as upon investors in those patents, it is less apparent that an unrestrained opinion could have a devastating effect upon inventors and investors in other industries where the technologies depend upon the isolation, purification or distillation of molecules. Technologies involving: flavorings; fragrances; energy and petrochemicals; and vitamins and nutritional supplements are all at risk.

Any *post hoc* exclusion of subject matter would send a chilling, if not devastating, message to all inventors and investors who may have spent considerable time and/or money to obtain and commercialize a patent. Indeed, normal patent prosecution takes two to three years. Some patent prosecutions have lasted decades. *See, e.g. Symbol Technologies, Inc. v. Lemelson Medical, Education & Research Foundation, LP*, 422 F.3d 1378, 1386, *amended*, 429 F.3d 1051 (Fed. Cir. 2005)) (Fourteen of Jerome H. Lemelson's issued patents were prosecuted over an 18-39 year period but were ultimately invalidated for prosecution laches).[12]

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[12] Like Lemelson's prosecution of his patent applications, the Petitioners herein have let many years lapse before bringing their Complaint to invalidate Respondents' patents.

4. Other federal departments and agencies recognize that isolated DNA is patentable subject matter because they are assignees of patents containing claims for isolated DNA.

Not only has the PTO issued thousands of patents for isolated DNA or nucleotide sequences,[13] but many of those patents have been assigned to other agencies and departments within the federal government including the Department of Health and Human Services[14] (including the Center for Disease Control[15]), and the Army.[16] The expressed position of the United States, as *amicus curiae*, is not consistent with the receipt of such assignments. U.S. Brief at 5, 10, 20-33. Those assignments belie any argument

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Consequently, relief should be denied under either a laches or failure to prosecute theory.

[13] *See* Resp. Brief at 28, 30.

[14] *See, e.g.*, U.S. Pat. No. 8,148,082, Claim 1 ("An isolated nucleic acid molecule that encodes a PTC taste receptor, or non-transmembrane fragment thereof, comprising at least 14 nucleotides of SEQ ID NO: 1 or SEQ ID NO: 3, wherein the nucleic acid molecule comprises nucleotide 145 of SEQ ID NO: 1 or SEQ ID NO: 3.").

[15] *See, e.g.*, U.S. Pat. No. 7,220,852, Claim 1 ("An isolated nucleic acid molecule consisting of the nucleotide sequence as set forth in SEQ ID NO: 1."); U.S. Pat. No. 8,119,788, Claim 1 ("An isolated nucleic acid molecule consisting of the nucleic acid sequence as set forth in SEQ ID NO: 1 or 2."); and Claim 13 ("An isolated nucleic acid molecule consisting of the nucleic acid sequence as set forth in SEQ ID NO: 1 or 2, wherein the nucleic acid is labeled.").

[16] *See, e.g.*, U.S. Pat. No. 7,029,853, Claim 1 ("An isolated and purified DNA fragment from chromosomal DNA of *B. anthracis* consisting essentially of the nucleotide sequence of SEQ ID NO:5.").

that "isolated DNA" is not patentable as a "composition of matter" pursuant to section 101.[17]

II. PATENT CLAIMS LIMIT AN INVENTOR'S EXCLUSIVITY RIGHTS AND JUDICIAL REVIEW OF THE PATENT.

The axiom that "claims claim," is a principle that is at the heart of the United States' patent system. This is evident throughout Title 35, throughout the rules promulgated pursuant to Title 35, and throughout the MPEP. It is also evident in the decisions of this Court and the Federal Circuit. Claims define what an inventor applies for, what examiners examine, and what the PTO ultimately grants to an inventor. Most importantly, claims specify the boundaries of the patented subject matter for which exclusivity is granted, providing notice of those boundaries both to the inventor and to the rest of the world. Moreover, when a court determines the validity or infringement of a patent, the *res* or object of the dispute is the claims, as issued.

Amici suggest that because the word "claim(s)" pervades the patent laws, regulations and examination procedures, the Respondents' Claims, as issued, is the appropriate starting point and ending point for the Court's analysis. *Amici* further suggest that because the "human gene" is not congruent with the isolated DNA in Respondents' Claims, Petitioners have asked the Court to respond to an abstract legal question, which the Court is not empowered to answer.

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[17] Furthermore, the United States, as an assignee of the '282 Patent, expressly recognizes the patentability of isolated DNA.

A. Claims Provide the Metes and Bounds of an Inventor's Exclusivity Rights.

According to the PTO, "The claims define the property rights provided by a patent, and thus require careful scrutiny. The goal of claim analysis is to identify the boundaries of the protection sought by the applicant and to understand how the claims relate to and define what the applicant has indicated is the invention." MPEP § 2103(I)(C).

One treatise regarding practicing before the Federal Circuit has elaborated on this point.

> A claim in a patent provides the metes and bounds of the right the patent confers on the patentee to exclude others from making, using, or selling the protected invention. The words of a claim describe and point out the invention by a series of limiting words or phrases – "limitations." **A court may not disregard claim limitations and effectively rewrite the claims**, nor may it read narrow claim limitations into broader claims, whether to avoid invalidity or to escape infringement. Without these fundamental rules, the court fears, the entire statutory and regulatory structure governing the drafting, submission, examination, allowance, and enforceability of claims would crumble.

Robert L. Harmon, Cynthia A. Homan, and Charles M. McMahon, PATENTS AND THE FEDERAL CIRCUIT 18 (10th Ed. 2011) (footnotes omitted, emphasis added).

> After all, the claims, not the specification, provide the measure of the patentee's right to exclude. Indeed, the claims of a patent are the

> sole measure of the patent grant. Once they issue in a particular form, the protected invention is, as a matter of law, that form. The disclosure of a patent is in the public domain, save as the claims forbid. **The claims alone delimit the right to exclude**; only they may be infringed.

Id. at 10 (footnotes omitted, emphasis added).

B. The Use of the Word "Claims" in Title 35, Patent Regulations, and MPEP Delimit a Patentee's Exclusivity Rights.

1. Claims are a focus, if not the central focus, of Title 35.

Although this case has been presented as a question of whether a "human gene" is patentable subject matter under Section 101, Section 101 explicitly incorporates all the requirements and conditions of Title 35. Section 101 provides: "Whoever invents or discovers any new and useful process, machine, manufacture, or any composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, ***subject to the conditions and requirements of this Title***." 35 U.S.C. § 101 (emphasis added). Many of the conditions and requirements expressly refer to a patent's "claims". The word "claim" or "claims" is found either explicitly or implicitly in sections regarding the patent application, § 111, regarding the "specification" and "claims", § 112, regarding the applicant's oath, § 115, and even regarding the fees for submitting an application, § 41.

Section 112 provides that "[t]he specification shall conclude with one or more **claims** particularly pointing out and distinctly **claiming** what the applicant regards as his invention." 35 U.S.C. § 112 (emphasis added).

The Court may also wish to note that Congress has expressly provided that if some claims within a patent are found to be invalid, the remainder of the claims may still be enforced. Section 288 provides, in part, "[w]henever a **claim** of a patent is invalid, an action may be maintained for the infringement of a **claim** of the patent which may be valid...." 35 U.S.C. § 288 (emphasis added).

2. Claims are at the core of the patent examination process and of the rights granted.

Section 2(b)(2)(A) of Title 35 provides: "The [Patent and Trademark] Office ... may establish regulations, not inconsistent with law, which – shall govern conduct of proceedings in the Office." Pursuant to this congressionally delegated authority, the PTO has promulgated numerous regulations regarding or referring to patent "claims". First and foremost is Rule 1.75 entitled "Claims".

Patent Rule 1.75(a) basically reiterates 35 U.S.C. §112. Rule 1.75(a) provides: "The specification must conclude with a **claim** particularly pointing out and distinctly **claiming** the subject matter which the applicant regards as his invention or discovery." 37 C.F.R. §1.75(a) (emphasis added).

Rules regarding the "application", *id.* at §1.51(b), the "oath", *id.* at §1.63(b)(2), and the "fees", *id.* at §1.16, also emphasize patent "claims".

Rule 1.104 is directed to the patent examination process. Subsection (a)(1) provides: "On taking up an application for examination ..., the examiner shall make a thorough study thereof and shall make a thorough investigation of the available prior art relating to the subject matter of the **claimed invention**." 37 C.F.R. §1.104(a)(1) (emphasis added). Subsection (c)(1) provides: "If the invention is not considered patentable, or not considered patentable **as claimed, the claims, or those considered unpatentable** will be rejected." 37 C.F.R. §1.104(c)(1) (emphasis added).

3. Sections 2103 *et seq.* of the MPEP confirm that claims are at the core of the patent examination process and delimit the inventor's rights.

Sections 2103 *et seq.* are directed towards the patent examination process. In conducting an examination, great emphasis is placed on the claims. "[E]ach claim should be reviewed for compliance with every statutory requirement for patentability in the initial review of an application, even if one or more of the claims is found to be deficient with respect to some statutory requirement." MPEP §2103(I).

Subsection 2103(I)(C) discusses how examiners are to review claims. It begins:

> The claims define the property rights provided by a patent, and thus require careful scrutiny. The goal of claim analysis is to identify the

> boundaries of the protection sought by the applicant and to understand how the **claims relate to and define what the applicant has indicated is the invention.** USPTO personnel must first determine the scope of a claim by thoroughly analyzing the language of the claim before determining if the claim complies with each statutory requirement for patentability. See *In re Hiniker Co.*, 150 F.3d 1362, 1369 ... (Fed. Cir. 1998) ("**[T]he name of the game is the claim.**").

MPEP §2103(I)(C) (emphasis added).

Section 2105 of the MPEP is particularly relevant. It is entitled "Patentable Subject Matter – Living Subject Matter." It provides:

> The decision of the Supreme Court in *Diamond v. Chakrabaty*, 447 U.S. 303 ... (1980), held that microorganisms produced by genetic engineering are not excluded from protection by 35 U.S.C. §101. It is clear from the Supreme Court decision and opinion that the question of whether or not an invention embraces living matter is irrelevant to the issue of patentability. **The test set down by the Court for patentable subject matter in this area is whether the living matter is the result of human intervention.**

MPEP §2105 (emphasis added). This section sets forth the PTO's interpretation of the *Chakrabaty* decision and guidelines to be used in interpreting Section 101 of Title 35. Quoting *Chakrabaty*, MPEP §2105(2), says:

> **In choosing such expansive terms as ... "composition of matter," modified by the comprehensive "any", Congress plainly contemplated that the patent laws would be given wide scope.**

MPEP §2105 (emphasis added).

Two years ago, Congress prohibited the patenting of human organisms. Section 33 of the Leahy-Smith America Invents Act ("AIA"), Pub. L. 112-29, 125 Stat. 264, §33 (2011) ("Notwithstanding any other provision of law, no patent may issue on a claim directed to or encompassing a human organism."). This prohibition is, however, not directed to isolated DNA, DNA, or even genes. The prohibition covers entire human organisms including embryos and fetuses. MPEP §2105 explains:

> The legislative history of the AIA includes the following statement, which sheds light on its meaning of this provision:
>
> [T]he U.S. Patent Office has already issued patents on genes, stem cells, animals with human genes, and a host of non-biologic products used by humans, but it has not issued patents on claims directed to human organisms, including embryos and fetuses. My amendment would not affect the former, but would simply affirm the latter.

MPEP § 2105 (quoting 157 Cong. Rec. E1179 (June 23, 2011) (Statement of Christopher H. Smith (NJ) incorporating Speech of Representative Dave Weldon on November 22, 2003)). Representative Smith expanded upon how this amendment should be construed. He said:

> **This amendment should not be construed to affect claims directed to or encompassing** subject matter other than human organisms, including but not limited to claims directed to or encompassing the following: cells, tissues, organs, or other bodily components that are not themselves human organisms (including, but not limited to, stem cells, stem cell lines, **genes**, and living or synthetic organs); hormones, proteins, or other substances produced by human organisms ...

157 Cong. Rec. at E1180 (emphasis added).

Representative Lamar Smith (TX), the lead sponsor of the AIA in the House of Representatives, explicitly recognized the patentability of nucleic acids. He said.

> The Committee recognizes that the economic viability of the biotechnology industry requires that patents be available for the full spectrum of innovation that may be subject to commercialization. The legislation, accordingly does not limit patent eligibility for any type of biotechnology invention that may be commercialized in the United States. The Committee also recognizes that continued innovation in the biomedical and biotechnological fields will lead to new kinds of inventions, and it expects that the overwhelming majority of such inventions will not raise any of the concerns that the present legislation addresses. **In particular, nothing in this section should be construed to limit the ability of the PTO to issue a patent containing claims directed to or encompassing:**

> 1. **any chemical compound or composition,** whether obtained from animals or human beings or produced synthetically, and whether identical to or distinct from a chemical structure as found in an animal or human being, **including but not limited to nucleic acids,** polypeptides, proteins, antibodies and hormones ...."

157 Cong. Rec. at E1183 (emphasis added).

MPEP Sections 2171, 2172 and 2173 confirm that patent claims set forth the boundary between an inventor and the public regarding the protected subject matter. These sections also confirm that it is the inventor who specifies, in the patent claims, what is to be patented.

C. According to this Court and the Federal Circuit, Claims Provide the Metes and Bounds of an Inventor's Exclusivity Rights.

In *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996), this Court provided a historical perspective on the evolution of modern claims practice.

> [A]s early as 1850 "judges were ... beginning to express more frequently the idea that in seeking to ascertain the invention 'claimed' in a patent **the inquiry should be limited to interpreting the summary, or 'claim'** ....

Id. at 378-379 (emphasis added, citations omitted).

The Federal Circuit, in *Markman,* had even more explicitly made the point that "***[t]he written description part of the specification does not delimit the right to exclude. That is the purpose and function***

***of the claims.*"** *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 980 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996) (emphasis added).

Almost two centuries ago, this Court made it abundantly clear that Congress required the specification to include a portion which the inventor "shall particularly specify and point out the part, improvement, or combination, which he claims as his own invention or discovery." *Merrill v. Yeomans*, 94 U.S. 568, 570 (1876) (concerning an early version of the patent statute, the Act of July 4, 1836).

More recently, the Court said: "The [patent] monopoly is a property right; and like any property right, its boundaries should be clear. This clarity is essential to promote progress, because it enables efficient investment in innovation. A patent holder should know what he owns, and the public should know what he does not." *Festo Corp. v. Shoketsu Kinzoku Kabushiki Co.*, 535 U.S. 722, 730-31 (2002).

In 2005, the Federal Circuit held *en banc* that "[i]t is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (*en banc*), *cert. denied*, 546 U.S. 1170 (2006) (internal quotations and citations omitted). Referring to 35 U.S.C. § 112, ¶ 2, the Chief Judge of the Federal Circuit said: **"[b]ecause claims delineate the patentee's right to exclude, the patent statute requires the scope of the claims be sufficiently definite to inform the public of the bounds of the protected invention, i.e., what subject matter is covered by the exclusive rights of the patent."** *Halliburton Energy Services, Inc. v. M-*

1, LLC, 514 F.3d 1244, 1249 (Fed. Cir. 2008) (emphasis added, citations omitted) (Michel, C.J.).

In a number of cases, the Federal Circuit has stated: "An essential purpose of patent examination is to fashion claims that are precise, clear, correct and unambiguous. Only in this way can uncertainties of claim scope be removed, as much as possible, during the administrative process." *See e.g., In re Buszard*, 504 F.3d 1364, 1366 (Fed. Cir. 2007) (quoting *In re Zletz*, 893 F.2d 319, 322 (Fed. Cir. 1989)).

In short, *Amici* believe that this Court should examine the Respondents' Claims as issued and not examine the "human gene."

D. Having Ignored the Respondents' Claims, Petitioners Have Asked the Court to Issue an Advisory Opinion which Is Beyond the Court's Power.

Although the Petitioners presented three questions to the Court, only their first question is before the Court. That question is: "Are human genes patentable?"

Amici believe that there is no case or controversy. A comparison of a "human gene" to the isolated DNA in the Respondents' Claims reveals that they are not the same and that by examining a human gene, the Court would only be responding to an abstract legal question.

Thus, the first question for this Court, like any court, is whether or not it has jurisdiction to hear the case. As this Court has explained, "'[n]o principle is more fundamental to the judiciary's proper role in our system of government than the constitutional limitation of federal-court jurisdiction to actual cases or controversies.'" *Raines v. Byrd*, 521 U.S. 811, 818 (1997) (internal citation omitted). Furthermore, "[t]he Court has recognized that the case-or-controversy limitation is crucial in maintaining the tripartite allocation of power set forth in the Constitution." *DaimlerChrysler Corp. v. Cuno*, 547 U.S. 332, 341 (2006) (internal quotation marks and citations omitted).

Because "[t]he Supreme Court is not empowered to decide abstract propositions ..." *Webster v. Reproductive Health Services*, 492 U.S. 490, 507 (1989) (quoting *Tyler v. Judges of Court of Registration*, 179 U.S. 405, 409 (1900)), it may not hear this case.

CONCLUSION

For the foregoing reasons, the Court should either affirm the decision below or withdraw certiorari as having been improvidently granted.

Respectfully submitted,

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Dated: March 14, 2013

AMICUS
CURIAE
BRIEF

No. 12-398

IN THE
Supreme Court of the United States

ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,
Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,
Respondents.

ON WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

BRIEF FOR AMICUS CURIAE THE BIOTECHNOLOGY INDUSTRY ORGANIZATION IN SUPPORT OF RESPONDENTS

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BRIEF FOR AMICUS CURIAE THE BIOTECHNOLOGY INDUSTRY ORGANIZATION IN SUPPORT OF RESPONDENTS

INTEREST OF AMICUS CURIAE[1]

The Biotechnology Industry Organization (BIO) is the country's largest biotechnology trade organization, representing over 1100 companies, academic institutions, and biotechnology centers in all 50 States and countries around the world. Myriad Genetics, Inc. is not a member of BIO.

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[1] No counsel for a party authored this brief in whole or in part, and no persons or entities, other than amici or their counsel, made a monetary contribution to the preparation or submission of this brief. Letters consenting to the filing of this brief are on file with the Clerk of the Court.

BIO members undertake research and development of biotechnological healthcare, agricultural, environmental, and industrial products. BIO members range from start-up businesses and university spin-offs to Fortune 500 corporations. The vast majority of BIO's members are small companies that have yet to bring products to market or attain profitability, and thus rely heavily on venture capital and other private investment. Patents on isolated DNA molecules and other isolated molecules are frequently critical to a biotech company's ability to attract the investment necessary for development of therapeutic, diagnostic, environmental, renewable energy, and agricultural products. The question presented in this case is thus of great importance to BIO's members.

PRELIMINARY STATEMENT

This lawsuit was brought as a test case intended to elicit a sweeping new exception to the subject matter eligible for patent protection under 35 U.S.C. § 101. Petitioner, Harry Ostrer, argues that without such an exception Myriad's patents will block access to genetic testing.[2] But the composition-of-matter claims that remain in this suit do not have the preemptive effect that Ostrer alleges, and Ostrer's exaggerated allegations provide no basis for this Court to deviate from decades of precedent and PTO practice.

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[2] The Federal Circuit held that Ostrer is the only plaintiff with standing. Pet. App. 31a-39a. Because this Court declined to grant certiorari on whether the remaining plaintiffs have standing, Ostrer is the sole petitioner before this Court.

Ostrer made a deliberate strategic decision not to seek relief on all the grounds available to him. He could have asked for a declaration of non-infringement or challenged the validity of Myriad's patents under 35 U.S.C. §§ 102, 103, or 112. Instead, he chose to pursue a legal theory with the greatest potential impact on the greatest number of patents. This Court should not allow Ostrer's all-or-nothing litigation strategy to push it into adopting an overbroad and unnecessary rule.

The exception to the Patent Act that Ostrer proposes would create tremendous uncertainty for a wide range of inventions. Isolated DNA molecules are used for many purposes besides diagnostic testing, including the production of therapeutic proteins, DNA-based vaccines, food safety, agriculture, and industrial and environmental uses. Ostrer's rule would also chill investment in isolated molecules other than DNA, such as RNA, antibiotics, antibodies, and enzymes.

The biotechnology community has invested many billions of dollars in researching, developing, commercializing, patenting, and licensing such inventions, in direct reliance on the PTO's considered decisions to issue thousands of patents on isolated DNA and other isolated molecules over the last two decades. If any exception is to be made to the statute's scope and the PTO's longstanding practice, it should be made by Congress on a prospective basis, where competing policy interests can properly be weighed and accommodated. This is particularly true where, as here, Congress has already declined to create the exception that Ostrer seeks, and where such a change would make the United States the only developed country to take such a restrictive view of patent eligibility—a result with potentially grave consequences for America's global economic and scientific leadership in biotechnology.

SUMMARY OF ARGUMENT

Now that Myriad's diagnostic method claims have been invalidated, it is far from clear that Ostrer has standing to challenge the remaining composition-of-matter claims. The case is further complicated by conflicting claim construction arguments and unresolved factual disputes. The most prudent course would be for the Court to remand for resolution of these issues.

If the Court presses ahead, it should affirm the judgment of the Federal Circuit. Whether the subject matter of Myriad's composition-of-matter claims is eligible for patent protection is not an abstract question of policy for this Court to decide. Congress defined the boundaries when it enacted the broad language of 35 U.S.C. § 101. Ostrer has never disputed that isolated DNA molecules fall within the plain meaning of that provision. These molecules were "composed," "manufactured," and "improved" over what existed in nature. This transformation in form as a direct consequence of human intervention results in molecules with a significantly different character and use compared to genes within their native setting. For example, unlike native genes, DNA amplified and isolated in the lab is not packed around and bonded to scaffolding proteins such as histones that control its function and does not have the epigenetic modifications such as methylation that play a critical role in regulating the expression of native genes. As a result of these differences and others, isolated DNA works for applications that would not be possible with native DNA.

The broad "product of nature" exception that Ostrer asks this Court to adopt would have harmful consequences for the biotechnology industry. It would chill a wide range of important activities that benefit society, including non-diagnostic uses of isolated human DNA, the untapped potential of isolated non-human DNA, the use of RNA molecules such as microRNA, and the invention and disclosure of other isolated molecules with natural analogues, such as therapeutic proteins and antibiotics. Complementary DNA (cDNA) patents are not sufficient to protect all of these innovations.

Ostrer's assertions regarding the scope and preemptive effect of Myriad's composition-of-matter claims are unsupported and based on an overly broad reading of the claims, presented for the first time in this Court. The Court should not accept Ostrer's construction of those claims nor allow Ostrer's exaggerated assertions about the preemptive effect of patents on isolated DNA molecules to drive its decision. The patent system is a carefully crafted bargain, and the sweeping change proposed by Ostrer is certain to have unintended consequences. Those consequences and the reliance interests of the industry should be given heavy weight in the Court's analysis.

ARGUMENT

I. THE COURT SHOULD REMAND FOR ADDITIONAL PROCEEDINGS ON STANDING AND CLAIM CONSTRUCTION

The briefing and procedural posture of this case have left the Court in a difficult situation. Before the Court can reach the merits, it must first decide whether Ostrer, the one petitioner found to have standing, still has standing to pursue this case. That requires the Court to consider not only the impact of its recent decision in *Clapper* v. *Amnesty International USA*, 133 S. Ct. 1138 (2013), but also serious questions about whether Ostrer's contemplated course of conduct would even infringe Myriad's remaining claims. Ostrer has studiously avoided any factual explanation of the testing he wishes to undertake. Further, as discussed below, Myriad's broad diagnostic method claims have already been invalidated, and the composition-of-matter claims that remain present little or no obstacle to genetic testing. *See infra* pp. 30-31. Thus, it is far from clear that a live case or controversy remains.

The situation is further complicated by the fact that even at this late date there is no agreement on what Myriad's claims actually cover. Many of Ostrer's assertions about the preemptive effect of Myriad's claims are based on claim construction arguments that were never made below and, in fact, contradict arguments that Ostrer made in the district court. *See infra* p. 31. The Court has also been presented with conflicting scientific arguments, many of which depend on questionable claim constructions. *See, e.g.*, Lander Br. 12-18 (referring to fragments of DNA in the body as "isolated"). And because the case arises on summary judgment, the Court must work its way through all of these disputes without resolving any issues of material fact.

In the face of this daunting task, the most prudent course would be for the Court to remand the case to the district court for further proceedings on standing and claim construction, along with the resolution of any factual disputes. The issues addressed in this case are too important to be decided without a record of the testing that Ostrer wants to conduct, a clear understanding of what Myriad's claims actually cover, and proper factfinding on disputed issues.

II. Isolated DNA Molecules Are Patentable Subject Matter

If the Court reaches the merits, it should affirm the judgment of the Federal Circuit.

A. Congress Defined The Scope Of Patent-Eligible Subject Matter Broadly To Include Anything Composed Or Manufactured By Humans

This Court has cautioned that "courts should not read into the patent laws limitations and conditions which the legislature has not expressed." *Diamond* v. *Chakrabarty*, 447 U.S. 303, 308 (1980) (internal quotation marks omitted). Strikingly, Ostrer and his amici barely mention the text of 35 U.S.C. § 101 and engage in no meaningful analysis of the words that Congress chose to define the subject matter that is eligible for patent protection if all the other requirements of patentability are met.

Section 101 states: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." Rather than asking whether Myriad's DNA claims are drawn to "products of nature," the statute in the first instance requires this Court to determine whether they are drawn to new and useful articles of "manufacture," or "composition[s] of matter," or "improvement[s] thereof." *See also* PTO, *Utility Examination Guidelines*, 66 Fed. Reg. 1092, 1095 (Jan. 5, 2001).

This was precisely the approach taken by this Court in *Chakrabarty*. *Chakrabarty* stated that the question before the Court was a narrow one of statutory interpretation" that required the Court to determine whether the claimed "micro-organism constitute[d] a 'manufacture' or 'composition of matter' within the meaning of the statute." 447 U.S. at 307. The Court began its textual analysis by noting that the term "manufacture" refers to materials given "new forms, qualities, properties, or combinations," while "composition of matter" means "all compositions of two or more substances" or "composite articles." *Id.* at 308 (internal quotation marks omitted). The Court further noted that "[i]n choosing such expansive terms as 'manufacture' and 'composition of matter,' modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope." *Id.*

Chakrabarty's discussion of the line between patent-eligible and patent-ineligible subject matter followed naturally from this textual analysis. The Court noted that Chakrabarty's claims were drawn "not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter." 447 U.S. at 309. This Court's pronouncement that "a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter" similarly distinguished between "'manifestations of ... nature'" that are untouched by human hands and the subject matter specified in 35 U.S.C. § 101, which includes anything with physical form that is composed, manufactured, or otherwise "'made by man.'" *Id.*[3]

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[3] Consistent with this distinction, in *Funk Brothers Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 131 (1948), each species of bacteria "infect[ed] the same group of leguminous plants which it always infected," "[n]o species acquire[d] a different use," and "[t]he combination of species produce[d] no new bacteria, no change in the six species of bacteria, and no enlargement of the range of their utility." "Each species ha[d] the same effect it always had"

In *J.E.M. Ag Supply, Inc.* v. *Pioneer Hi-Bred International, Inc.*, 534 U.S. 124 (2001), the Court reiterated the importance of focusing on the words chosen by Congress. The Court once again noted the breadth of the subject matter eligible for patent protection if the other requirements of the statute are met. *Id.* at 130-131. The Court further explained that even if *Chakrabarty* did not address the precise question before it, it remained highly relevant to "the question whether sexually reproduced plants fall within the subject matter of § 101" because "*Chakrabarty* broadly interpreted the reach of § 101." *Id.* at 131 n.2; *see also id.* at 131 ("The subject-matter provisions of the patent law have been cast in broad terms to fulfill the constitutional and statutory goal of promoting 'the Progress of Science and the useful Arts[.]'"); *id.* at 137 n.9 ("[T]he statutory terms 'manufacture or composition of matter' ... have been interpreted broadly to evolve with developments in science and technology."). Notably, no one "dispute[d] that plants otherwise fall within the terms of § 101's broad language that includes 'manufacture' and 'composition of matter.'" *Id.* at 131-132.

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and "serve[d] the ends nature originally provided and act[ed] quite independently of any effort of the patentee." *Id.*

In addition, *Funk Brothers* turned on the conclusion that the combination of non-inhibitive species "fell short of invention." 333 U.S. at 131. In 1952, Congress eliminated that mode of analysis and replaced it with Section 103, which focuses on whether an invention was obvious to one of skill in the art at the time of invention. As explained by Judge Rich, one of the 1952 Act's principal drafters, "'[i]nvention' was that 'beautiful uncertainty in the law' from which the patent bar made its living—practicing what was essentially a mystery." Rich, *Why and How Section 103 Came To Be*, 14 Fed. Cir. B.J. 181, 187 (2004). "Section 103 was enacted as a much better tool for the job." *Id.* at 192.

The isolated DNA molecules at issue in this case likewise fall within the terms of the statute and exist only as a result of human intervention. These molecules were "compos[ed]," "manufacture[d]," and "improve[d]" over what existed in nature—not merely "discovered" or "found." This transformation in form as a direct consequence of human intervention gives the molecules new utility not shared by native DNA and brings them squarely within the scope of patent-eligible subject matter defined by Congress.

B. Isolated DNA Molecules Are New Compositions Of Matter Made By Human Ingenuity

An isolated DNA molecule is not merely "information" or abstract knowledge like a mathematical formula.[4] It is a molecule composed of specific nucleotide bases linked together through a sugar-phosphate backbone. Not only is that molecule chemically distinct from native DNA as a result of human intervention, but as a practical matter, isolated DNA is synthesized in a laboratory rather than extracted from a natural source.

1. Human DNA in its natural or "native" form exists as part of chromosomes within the nucleus of human cells. Chromosomes are complex, stable structures consisting of extremely long strands of DNA chemically bonded to numerous proteins (such as histones), which give the chromosome compact form, regulate gene function, and account for half the molecular mass of the chromosome. Watson et al., *Molecular Biology of the Gene* 135 (6th ed. 2008). Shorter sequences of nucleotides within each chromosome form functional units called "genes."

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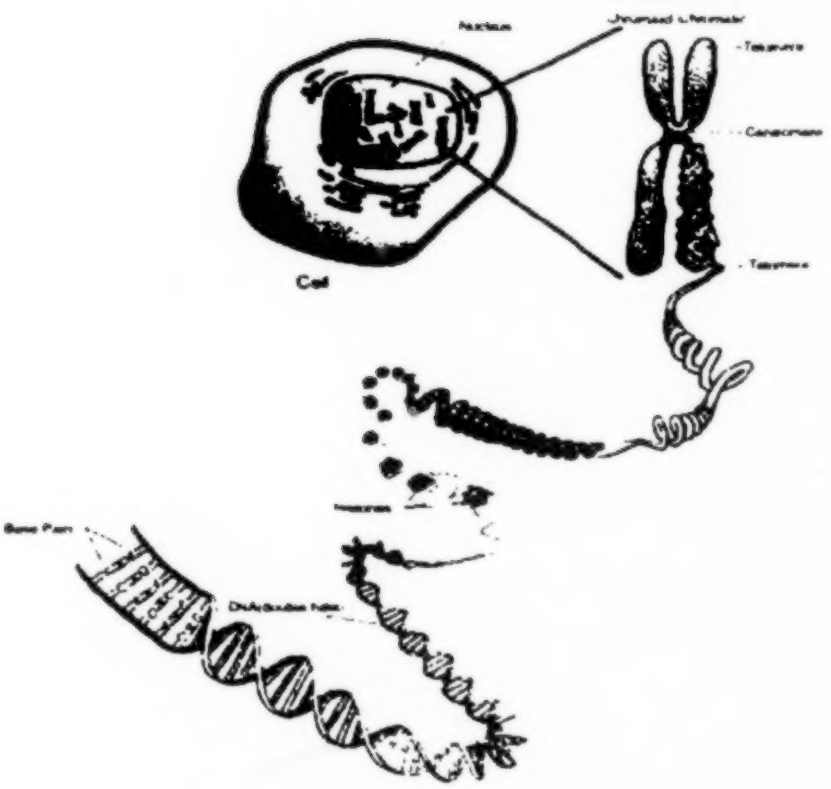
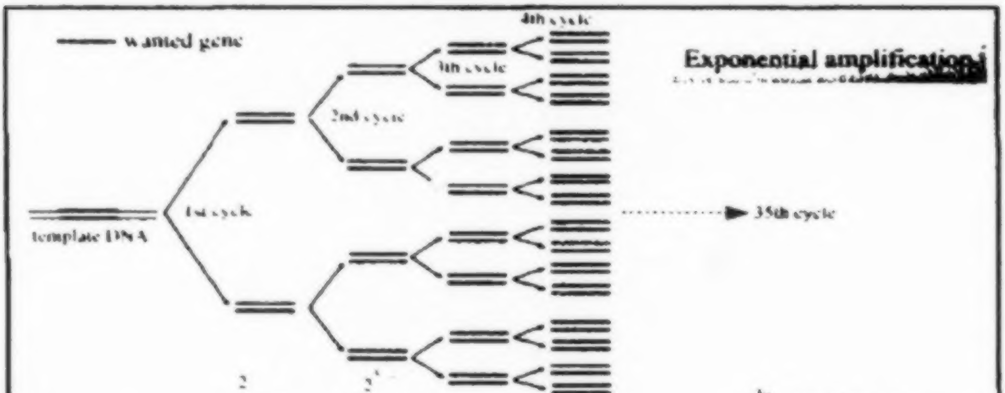
[4] The term "isolated DNA" as used in this section refers to an isolated DNA molecule that is separate from chromosomal proteins and from whole genome DNA extracted from the body.


Chromosome
Nucleus
Telomere
Centromere
Telomere
Cell
Histones
Base Pairs

National Human Genome Research Institute, *Chromosome*, http://www.accessexcellence.org/RC/VL/GG/nhgri_PDFs/chromosome.pdf.

The notion that isolated DNA is cleaved and extracted from the human genome is inaccurate and is based on a misunderstanding of how DNA is isolated in the real world. It is true that raw, whole genome DNA can be extracted from a biological sample and cleaved into random fragments of DNA and that a gene of interest might constitute a vanishingly small fraction of this slurry of random DNA fragments, but this process does not result in the isolation of any particular gene. In fact, this sort of extraction and cleavage of genomic human DNA pre-dates Myriad's patents by many years and cannot be what the claims mean by isolated DNA.

Moreover, in order to study or use any particular DNA sequence it is necessary to isolate it from the mix, and this isolation invariably entails amplifying the gene of interest (typically a million-fold or more) using laboratory techniques that synthesize new DNA molecules using genetically engineered recombinant cells or cell-free biochemical methods such as polymerase chain reaction (PCR). *See* Genetic Science Learning, *PCR Virtual Lab*, http://learn.genetics.utah.edu/content/labs/pcr (PCR diagram at right). This process yields new and separate chemical compounds that were never extracted from nature and exist only because of human intervention.


wanted gene
template DNA
1st cycle
2nd cycle
3th cycle
4th cycle
Exponential amplification
35th cycle
2^2
4 copies
2^3
8 copies
16 copies
32 copies
2^{36} = 68 billion copies
(Andy Vierstraete 1999)

Vierstraete, *Principle of the PCR*, http://users.ugent.be/~avierstr/principles/pcr.html.

Isolated DNA molecules differ significantly from naturally-occurring DNA contained in larger chromosomes in multiple ways. *First*, isolated DNA molecules are typically much smaller than a full chromosome. For example the BRCA1 gene in its native form appears on human chromosome 17, which contains about 80 million base pairs. National Library of Medicine, *Chromosome 17*, http://ghr.nlm.nih.gov/chromosome/17. An isolated molecule with the same sequence as the BRCA1 gene, however, consists of only about 80,000 nucleotide pairs selected from this larger set. National Library of Medicine, *BRCA1*, http://ghr.nlm.nih.gov/gene/BRCA1.

Second, the complex spatial organization of native DNA, which is packed around and bonded to scaffolding proteins such as histones, dynamically affects its function and configuration. *See* Watson 192. Isolated DNA molecules are separated from the larger set of structures that make up the chromosome, eliminating these effects and—importantly—opening the molecules to a broader range of uses.

Third, native genes are covalently bonded to other DNA in the chromosome through phosphodiester bonds between the 5' phosphate group and the 3' hydroxyl group of adjoining nucleotides. *See* Watson 104. Isolated DNA is separated from other nucleotides, again opening it to new uses.

Fourth, in a human chromosome, the nucleotide subunits of native genes are extensively modified in a manner that regulates gene expression. *See* Watson 626-629. These "epigenetic" modifications, particularly methylation of cytosines, are lost during the synthetic processes inherent in the isolation of genes, rendering the isolated gene chemically and structurally distinct from any native gene.

2. The distinction between native and isolated DNA is even starker in the case of cDNA. cDNA molecules consist solely of exons, nucleotide stretches that contribute directly to the production of proteins. *See* Watson 415. cDNA does not occur naturally in the body; indeed, even the nucleotide sequence of a cDNA molecule has no analogue in native chromosomal DNA, where the nucleotide sequences are interrupted by introns. For example, the naturally-occurring BRCA1 and 2 genes each contain more than 70,000 nucleotides, while the exons that make up their corresponding cDNA molecules together have fewer than 16,000. Thus, the structure of the claimed isolated cDNA molecules differs substantially from that of the natural BRCA genes.[5]

3. The United States agrees that cDNA is not a product of nature but downplays the significance of creating isolated genomic DNA by saying that "[i]solated DNA is simply naturally occurring DNA that has been extracted from its cellular environment and separated from extraneous material." U.S. Br. 20. Dismissing these structural changes as insignificant, however, would set a dangerous precedent for biology and chemistry. Judge Lourie noted that generally speaking "a covalent bond is the defining boundary be-

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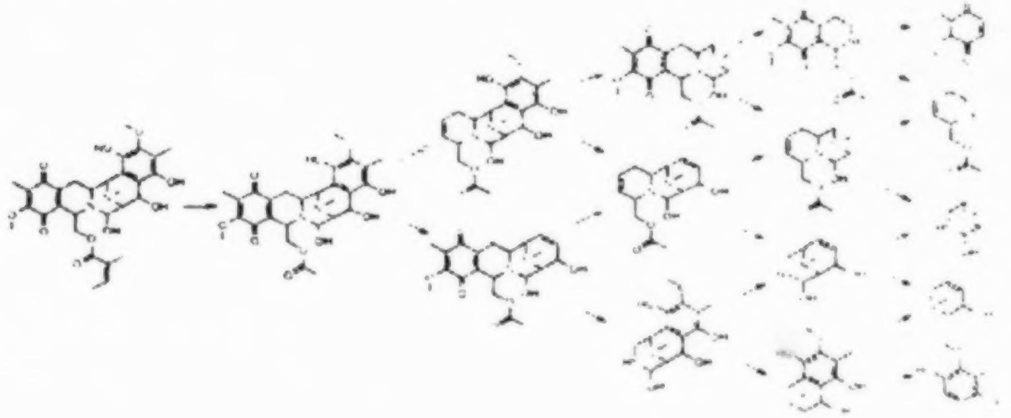
[5] Ostrer argues (at 51) that naturally-occurring "pseudogenes" within an organism's chromosomal DNA contain identical nucleotide sequences to cDNA molecules. But the record does not support that conclusion. One witness stated that nucleotide sequences in pseudogenes differed from cDNA sequences by at least 10 percent. JA658-659. Another referenced an example where only a portion of BRCA1 cDNA was contained in the chromosomal DNA as a pseudogene. JA675. And in both examples, the pseudogene sequences—unlike cDNA—remain fixed portions of the larger chromosomal sequence, not freestanding molecules.

tween one molecule and another." Pet. App. 48a. To equate an isolated DNA molecule with genomic DNA in the body would invite other attempts to equate distinct molecules merely because the structure of one might be found within the larger structure of the other.

For example, the diagram below shows just a few of the distinct molecules "contained" within the larger structure of Renieramycin P, a toxic molecule that naturally exists in certain marine sponges.



Over et al., *Natural-Product-Derived Fragments for Fragment-Based Ligand Discovery*, 5 Nature Chemistry 21, 22 fig.1 (2013).

Each of the molecules depicted is no more or less an extract from the natural molecule than isolated DNA is from native DNA. Characterizing isolated DNA as a product of nature would therefore create tremendous uncertainty by blurring the lines that have traditionally separated one molecule from another. It would also encourage attempts to recharacterize molecules long thought to be patentable subject matter as mere extracts of larger molecules in nature.

4. All of these structural differences easily distinguish isolated DNA molecules from the parade of hor-

ribles that Ostrer and his amici offer regarding the patenting of coal, gold, and kidneys. The mechanical extraction of these products from their natural environment does not involve the same degree of transformation that is achieved through the creation of isolated DNA molecules. Coal, gold, and kidneys start out relatively distinct from the environments in which they are found, particularly when compared to the task of selecting a small set of nucleotides from an otherwise vast chromosome. Removing them from their natural environments does not involve the same type of transformation to their three-dimensional structure that occurs when a DNA molecule is created without the histones and other scaffolding proteins that exist in the chromosome. Nor does their extraction break the same type of bonds that link native DNA.

The extraction of coal, gold, and kidneys also differs from the creation of isolated DNA in that the end product is simply the thing that has been removed from nature. By contrast, isolated DNA is typically a collection of new molecules that were replicated million-fold in the lab. The better analogy would thus be the production of "cloned" coal, "amplified" gold, or a "replicated" kidney produced in the lab from chemical building blocks.

Finally, it is important to note that examples like coal, gold, and kidneys obscure more than they illuminate because our instincts about these examples tend to be colored by the fact that these substances have been known for millennia or would be obvious. Both these reasons provide independent grounds for denying patent protection, *see infra* pp. 17-18, and the Court should not allow them to skew its analysis of the broad terms that Congress chose to define patent-eligible subject matter.

C. Isolated DNA Molecules Have New And Distinctive Properties And Uses Compared To Naturally-Occurring DNA

Isolated DNA and cDNA molecules have a significantly different character and use compared to genes within their native setting. In their natural form, genes are trapped in chromosomes and the other components of a cell. They are essentially inaccessible and under the control of the physiology of the organism in which they reside. Isolating a DNA molecule, in addition to creating a whole new chemical composition that does not exist in nature, imparts new utilities and functions unavailable from native DNA.

This enlarged range of utility flows not only from the fact of isolation but from the chemical changes that occur when DNA is synthesized in a laboratory, a process that does not reproduce the chemical and structural "epigenetic" modifications characteristic of native DNA, such as the spatial organization of native DNA around scaffolding proteins and the methyl groups on cytosine bases that play an integral role in the regulation of gene expression. *See supra* p. 13; Watson 192, 626-629. These differences are some of the reasons why isolated DNA works for applications that would not be possible with native DNA.

D. Section 101 Is A Blunt Instrument And There Are Other Tools For Limiting The Scope Of Patent Claims

The fact that isolated molecules derived from nature are patent-eligible subject matter does not mean that every such molecule can be validly patented. Section 101 plays an important screening function to prevent patents on things such as abstract ideas that do not fall within Section 101's plain terms. But after meeting that "threshold test," a claimed invention must also be "novel, see § 102, nonobvious, see § 103, and fully and particularly described, see § 112." *Bilski* v. *Kappos*, 130 S. Ct. 3218, 3225 (2010).

The Federal Circuit has rejected claims to isolated DNA molecules on grounds of anticipation, obviousness, lack of utility, and failure to comply with the requirements of 35 U.S.C. § 112. *E.g.*, *In re Gleave*, 560 F.3d 1331 (Fed. Cir. 2009) (patent to antisense DNA sequences denied as anticipated by prior art); *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009) (affirming PTO's obviousness rejection of a patent on a DNA molecule); *Regents of Univ. of Cal.* v. *Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997) (claim to a vertebrate cDNA sequence encoding insulin invalid for lack of written description); *In re Fisher*, 421 F.3d 1365 (Fed. Cir. 2005) (rejecting claims to expressed sequence tags—short DNA molecules of unspecified cellular function—for lack of sufficient utility).

Many of Ostrer's arguments are not addressed to the issue of patent-eligible subject matter at all but rather to these other doctrines. For example, Ostrer's allegation (at 14) that Myriad's claims "reach all uses of multiple compositions ... whether or not Myriad or anyone else has identified those compositions" is a classic written description argument under 35 U.S.C. § 112. *See Ariad Pharm., Inc.* v. *Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc) (the "specification does not satisfy the written description requirement if it fails to support the scope of the genus claimed"). The same is true of Ostrer's argument (at 15) that another claim "reaches any BRCA2 gene with harmful mutations regardless of whether another geneticist is the one who finds the mutation."

Ostrer's assertion (at 16) that "[f]ifteen (15) nucleotide sequences from the BRCA1 gene can be found in virtually every other gene in the body" is likewise misdirected. If that is true and the 15-nucleotide claims are as open-ended as Ostrer contends, Ostrer presumably could have brought an anticipation or obviousness challenge under 35 U.S.C. § 102 or § 103 long ago based on the prior isolation of molecules covered by the claims.

Ostrer made a deliberate strategic decision not to assert grounds of invalidity that would be specific to the challenged claims alone. Instead, his theory of the case is designed to make it impossible for the Court to invalidate these claims without also invalidating large numbers of other patents in areas that have nothing to do with diagnostic testing. The Court should not allow that strategic choice to pressure it into creating a sweeping exception to the scope of patent-eligible subject matter.

III. THE BROAD PRODUCT OF NATURE EXCEPTION THAT OSTRER SEEKS WOULD CHILL INNOVATION

A broad "product of nature" exception would have harmful consequences for the biotechnology industry and would chill a wide range of important activities that benefit society. Although this case has focused on the use of isolated human DNA for diagnostic purposes, the rule that Ostrer proposes could interfere with non-diagnostic uses of isolated human DNA, the untapped potential of isolated non-human DNA, and the invention and disclosure of other isolated molecules with natural analogues, such as therapeutic proteins and antibiotics. Ostrer's rule would also put the United States out of step with other major industrialized nations, which permit patents on isolated nucleic acids. *See* Institute of Professional Representatives Br. 3.

A. Ostrer's Proposed Rule Would Impact Non-Diagnostic Uses Of Isolated DNA

Isolated DNA molecules have been critical in developing a broad range of therapeutic, agricultural, food safety, and industrial technologies:

Therapeutic Proteins. Recombinant proteins are used to treat many diseases and conditions, including cancer, diabetes, growth deficiency, rheumatoid arthritis, hemophilia, and hepatitis. For example, Amgen's pioneering work with erythropoietin revolutionized the treatment of anemia. Twenty-five percent of renal patients on dialysis required regular blood transfusions before Amgen isolated the DNA that codes for erythropoietin and made it therapeutically available. Jelkmann, *Molecular Biology of Erythropoietin*, 43 Internal Med. 649, 649 (2004). Amgen's development and marketing of its therapeutic, Epogen®, virtually eliminated the need for such transfusions. Amgen's patent on the isolated DNA molecule for erythropoietin, U.S. Patent No. 4,703,008, has been critical in protecting this breakthrough. *E.g.*, *Amgen, Inc.* v. *Chugai Pharm. Co.*, 927 F.2d 1200 (Fed. Cir. 1991). Among other things, that patent claimed: "'A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.'" *Id.* at 1204.

Synthetic insulin is another success story. Insulin is a hormone that regulates blood sugar levels; diabetes results when the body stops producing insulin (type 1) or can no longer respond to it (type 2). Doctors once relied on insulin taken from the pancreases of slaughtered cows or pigs to treat diabetes. Genentech identified the DNA molecules necessary to produce and assemble synthetic human insulin in bacterial host cells. *See* Press Release, Genentech, *First Successful Laboratory Production of Human Insulin Announced* (Sept. 6, 1978). Unlike pig and cow insulin, synthetic insulin does not cause allergic reactions in human patients and is available in abundant quantities.

Human growth hormone (HGH) is a third vivid example of the advances made possible by isolated DNA molecules. The hormone used to be extracted from the pituitary glands of human cadavers. It was only after scientists synthesized HGH in a lab, using isolated DNA molecules to express the protein in bacterial cultures, and disclosed this invention to the world that HGH became available for wider therapeutic applications. *See, e.g.*, U.S. Patent No. 4,898,830 (claiming "[a] DNA molecule consisting of DNA encoding amino acids 1-191 of human growth hormone"). Recombinant HGH is now used to treat a variety of childhood and adult growth disorders. *E.g.*, Schambelan et al., *Recombinant Human Growth Hormone in Patients with HIV-Associated Wasting*, 125 Annals Internal Med. 873, 873 (1996).

Vaccination. By using DNA that encodes only certain proteins from the surface of a virus or bacteria, biotechnology innovators have been able to manufacture vaccines carrying a lower risk of infection and improved vaccine stability. *See* World Health Organization, Technical Report Series No. 941, *Guidelines for Assuring the Quality and Nonclinical Safety Evaluation of DNA Vaccines* 58 (2007). Vaccines that use small pieces of DNA to trigger antibody production also have the potential to provide immunization against microbes for which no vaccine is currently available. BIO, *Guide to Biotechnology* 37 (2008). The technology is still in its nascent stages, but the field is developing rapidly. There are currently over 40 clinical trials evaluating DNA vaccines for diseases such as HIV, influenza, hepatitis, malaria, and cancer. Ferraro et al., *Clinical Applications of DNA Vaccines: Current Progress*, 53 Clinical Infectious Diseases 296, 298 (2011).

Agriculture. Researchers continue to work on ways to feed more people at lower cost and with less environmental impact by identifying and using genetic markers associated with natural resistance to insects and diseases, resistance to environmental stresses such as drought and temperature fluctuations, and improved characteristics such as lower nutrient use and higher yield. Considerable investment is still required to unlock the full potential of DNA-based agriculture. For example, important genomes, such as the cow and chicken genomes, were not sequenced until 2004. *Guide to Biotechnology* 49. The corn genome, only the third of any major crop to be sequenced, was not completed until 2008. *Id.* 14.

Food Safety and Health. The importance of DNA-based inventions to the food supply does not end on the farm. "[R]esearchers are now using genomic technologies to drive improvements in food processing, food safety, and quality assurance." Brown & van de Ouderaa, *Nutritional Genomics: Food Industry Applications From Farm to Fork*, 97 Brit. J. Nutrition 1027, 1029 (2007). DNA technology holds great promise in combating foodborne illness, a major public health issue affecting millions of people each year. *See* Marchelli et al., *DNA Analyses in Food Safety and Quality, in Detection of Non-Amplified Genomic DNA* 25, 36 (Spoto & Corradini eds., 2012). DNA probes to detect harmful or lethal microorganisms in the food supply offer significant benefits over conventional detection methodology.

See Brown & van de Ouderaa, 97 Brit. J. Nutrition at 1030-1031. Biotechnology is also providing improved food products with health benefits to populations with limited healthcare options or challenging living conditions. For example, the addition of human milk components to livestock milk has the potential to benefit milk safety and production as well as animal health. *See* Maga et al., *Production and Processing of Milk from Transgenic Goats Expressing Human Lysozyme in the Mammary Gland*, 89 J. Dairy Sci. 518, 518 (2006).

Industrial and Environmental Biotechnology. Patents on isolated DNA molecules are also important for industrial, energy, and environmental applications. DNA-encoded biocatalysts, such as enzymes, can decrease energy use, replace harsh chemicals in industrial processing, and produce biofuels and green plastics without the use of petroleum, helping to reduce dependence on "dirty" energy sources and mitigate global climate change. *See* Shi, *Biotechnology: Healing, Fueling, and Feeding the World*, 9 Revs. Envtl. Sci. Biotech. 311, 311 (2010).

Engineering Tools. The laboratory techniques used to manufacture large quantities of proteins themselves rely on other isolated DNA molecules to promote and regulate the expression of the desired protein in a host cell. Isolated DNA molecules have thus become critical engineering tools.

Unforeseeable Discoveries. Just as important as the DNA-based research already in progress are the unforeseen discoveries that might never occur without strong patent protection to encourage investment of private capital.

Native DNA simply cannot be used in these applications. A rule that limits the patentability of isolated

DNA thus threatens to stifle research in a vast array of important fields.

B. cDNA Claims Are Inadequate To Protect Critical Inventions, Particularly Isolated Non-Human DNA And Isolated RNA Molecules

The United States and others urge this Court to draw a distinction between cDNA and isolated genomic DNA. One amicus even asserts that the "biotechnology industry would not be substantially affected" by a decision holding that only cDNA is eligible for patent protection. Lander Br. 27. Although cDNA is certainly an easy case, the assertion that patents on isolated genomic DNA are not important is simply wrong.

The effects of limiting patent eligibility to cDNA would fall particularly hard on non-human genetic research. Prokaryotes such as bacteria do not have introns. *See* Watson 136-143. The same is true for blue-green algae (a vast category of archaic bacteria) and many viruses. As a result, when an inventor creates an isolated DNA molecule inspired by one of the millions of unexplored genomes of these organisms, it is not possible to protect the invention with a cDNA patent because there are no introns for the inventor to exclude.

Research into the possible applications of isolated prokaryotic DNA has already yielded critical advances. The enzyme most commonly used to perform PCR was derived from a prokaryotic bacterium found in hot springs, *Thermus aquaticus*. Watson 380 fig.12-2. That foundational discovery—which made PCR practical as a laboratory technique, ushering in the modern era of molecular biology—was protected by a patent claiming the DNA sequence required to express a form of the enzyme. U.S. Patent No. 5,405,774. Prokaryotic

DNA has also been used to detect infectious diseases and to study bacteria that live in the human body. Finally, prokaryotes often serve as host cells to produce a desired protein, and prokaryotic DNA has become an important engineering tool to regulate or promote protein expression. Placing limits on patenting these regulatory elements would affect the ability to manufacture proteins from isolated DNA molecules of any origin

This field is still in its early stages. As of 2008, less than one percent of the world's microorganisms had been cultured and characterized. *Guide to Biotechnology* 64. Private investment will be critical to that effort and to identifying, isolating, and developing the innovative polynucleotides that will change the way we grow our food, fuel our cars, care for our environment, and even treat illness. A rule limiting patent eligibility to cDNA could cut off that research in its infancy.

cDNA claims are also insufficient to protect important inventions involving other nucleic acids, such as RNA, as well as the developing area of research focusing on gene regulation by intronic sequences. For example, microRNA (miRNA) is a small RNA molecule that does not encode proteins but plays a critical role in regulating gene expression. miRNAs have been linked to cancer, obesity, and heart disease in animal models. Clinical studies testing the use of miRNA as a therapeutic agent are currently underway, but without patent protection, it would be difficult to attract the necessary investment to fund this promising platform.

C. Ostrer's Rule Would Also Threaten A Wide Range Of Other Types Of Isolated Molecules

Just as it is important for the Court to look beyond human DNA and to consider not only diagnostic uses but also therapeutic, agricultural, and industrial uses, it is also important for the Court to consider the impact that Ostrer's proposed rule would have on the incentives to invent other molecules. Without patent protection, many new and useful compositions of matter that are isolated or derived from natural sources would never be discovered, disclosed, and commercialized. For example:

Sirolimus, also known as rapamycin, is a macrocyclic compound produced by the bacterium *Streptomyces hygroscopicus* NRRL 5491, which was first discovered in a soil sample from Easter Island. The inventor disclosed the discovery, deposited a sample of the bacterium, and applied for and obtained a patent on purified sirolimus as a novel antifungal and antibiotic compound. *See* U.S. Patent No. 3,929,992. The compound was subsequently developed as a powerful immunosuppressant for clinical use, and today RAPAMUNE® (sirolimus) is used to prevent organ rejection in kidney transplant patients. Sirolimus was also found to display cytostatic (antiproliferative) activity outside the immune system, and coronary stents with sirolimus-eluting coatings, such as Cordis's CYPHER® Stent, were developed to prevent endothelial growth around the newly placed stent. Semisynthetic derivatives of sirolimus have also been developed in an effort to use sirolimus's cell growth-arresting properties to treat cancer.

Tacrolimus is a compound with immunosuppressive properties that is used to help prevent the rejection of transplanted organs. Tacrolimus is produced by the bacterium *Streptomyces tsukubaensis*, which was first discovered in a soil sample in Japan. After isolating and applying for a patent on the compound, the inventors published their discovery and deposited samples of *Streptomyces tsukubaensis* No. 9993. On January 16, 1990, the PTO issued U.S. Patent No. 4,894,366 on tacrolimus. In 1994, the FDA approved the patent owner's commercial product Prograf®, which is used to prevent organ rejection in people who have received kidney, liver, or heart transplants. The '366 patent has now expired, and at least four companies have launched generic versions of Prograf®.

Aplidine, also known as dehydrodidemnin B, is a chemical compound that was first extracted from a sea squirt, *Aplidium albicans*. After isolating the compound, its inventors patented aplidine for use as a novel antitumor agent. U.S. Patent No. 5,834,586. The isolation of aplidine permitted it to be produced synthetically, and it is now in clinical trials as a treatment for several different types of cancer. *See* PharmaMar, *Products: Aplidin*®, http://pharmamar.com/aplidin.aspx. In 2004, the FDA granted Aplidin® orphan drug status for its potential use in treating multiple myeloma, a plasma cell cancer. 21 U.S.C. §§ 360aa *et seq.*; 21 C.F.R. pt. 316. Orphan drug status is a recognition that research and development of new treatments for this disease, given its rarity, would otherwise be prohibitively expensive. Uncertainty regarding the patentability of purified aplidine as an antitumor agent would have only exacerbated this problem.

Exenatide is a chemical compound first purified from a hormone found in the saliva of Gila monsters. It was developed and patented in 1993 by Dr. John Eng for use as a novel treatment for diabetes. U.S. Patent No. 5,424,286. It is now approved by the FDA for that purpose in both twice-daily and weekly forms, under the brand names Byetta® and Bydureon®, respectively.

Phytase, an enzyme included in animal feed, significantly reduces the inability of some livestock to digest phytate in grain, which causes environmental pollution from fecal phosphate. Progress in this area has been facilitated by the invention of a phytase enzyme from the microbe *E. coli* and patent protection of isolated DNA. *See* U.S. Patent No. 6,190,897.

Glucoamylase, an enzyme from the fungus *Trichoderma reesei* that efficiently releases glucose sugars from carbohydrates, allows for better production of biofuels such as ethanol. *See* U.S. Patent No. 7,413,887.

Muromonab-CD3, a monoclonal antibody derived from mice, is used to prevent transplant rejection by suppressing the human immune system and was created using standard immunization and hybridoma techniques. The inventors patented the resulting antibody, muromonab-CD3. *See, e.g.*, U.S. Patent No. 4,361,549. After further investment and clinical trials, muromonab-CD3 became the first monoclonal antibody approved by the FDA, and it was commercialized as Orthoclone OKT3®.

It is these real world examples, rather than the implausible ones offered by Ostrer, that the Court should keep in mind as it weighs the potential impact of its decision. No one would or could patent coal, gold, or kidneys. But an overbroad rule directed to eliminating that fanciful possibility would have real and lasting consequences for other areas of innovation that depend on patent protection. Every time the Court thinks about coal, it should think about antibiotics. Every time it thinks about gold, it should think about erythropoietin. Every time it thinks about kidneys, it should think about insulin, antibodies, DNA vaccines, industrial enzymes, early detection of foodborne illnesses, and all the other countless inventions that might never be made and disclosed without the incentives provided by the patent system.

IV. PATENTS ON ISOLATED DNA MOLECULES DO NOT IMPEDE THE PROGRESS OF SCIENCE OR HARM PATIENTS

A. Ostrer Exaggerates The Effect Of Myriad's Composition-Of-Matter Claims

Ostrer makes a series of sweeping—and demonstrably incorrect—assertions regarding the preemptive effect of Myriad's composition-of-matter claims. Those assertions provide no basis for deviating from decades of precedent and PTO practice recognizing the patent-eligibility of isolated DNA molecules.

1. As an initial matter, it would be a mistake for the Court to turn the preemption principle that the Court discussed in *Mayo* into the decisive test that Ostrer proposes. *See* Pet. Br. 40. This Court acknowledged in *Mayo* that "too broad an interpretation of [the preemption] principle could eviscerate patent law." *Mayo Collaborative Servs.* v. *Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1293 (2012). This case well illustrates the sort of speculation and collateral litigation that indiscriminately applying a preemption standard would require.

2. Ostrer contends that Myriad's claims "reach all uses of the two human genes" (Pet. Br. 42), and that "[t]he effect of the patents has been to prevent and deter research" (*id.* 43) and to "bar access to people's genetic information" (*id.* 44). These unsubstantiated allegations exaggerate the effect of the composition-of-matter claims before the Court.

Ostrer initially challenged two distinct sets of claims: broad diagnostic method claims directed to "comparing" or "analyzing" DNA sequences and the composition-of-matter claims at issue here. It was the first set of claims, not the second, that impacted genetic diagnostic testing. But those diagnostic method claims were invalidated even before this Court decided *Mayo*. Now that the diagnostic method claims have been invalidated, the remaining composition-of-matter claims are unlikely to have any effect on Ostrer, and certainly not the sweeping effect that Ostrer alleges.

The first set of claims (claims 1, 2, and 7 of U.S. Patent No. 5,747,282; claims 1, 6, and 7 of U.S. Patent No. 5,837,492; and claim 1 of U.S. Patent No. 5,693,473) are all directed to isolated DNA molecules comprising *thousands* of nucleotides. Conventional BRCA testing, however, is based on the amplification and analysis of much smaller fragments of DNA. *See, e.g.*, Cook-Deegan et al., *Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer*, 12 Genetics Med. S15, S23 (Apr. Supp. 2010). As Ostrer concedes (at 11 n.3), there is no need to create full-length molecules to engage in that testing.

The remaining two claims (claims 5 and 6 of the '282 patent) have broader scope because they cover isolated fragments having as few as 15 nucleotides. The breadth of such claims, however, makes them more susceptible to attack under 35 U.S.C. § 102 (anticipation), § 103 (obviousness), and/or § 112 (written description and enablement), avenues Ostrer intentionally disavowed. *See supra* pp. 18-19.

Moreover, existing and emerging sequencing techniques such as whole genome sequencing do not require isolation of the gene being sequenced. *See, e.g.*, Holman, *Will Gene Patents Derail the Next Generation of*

Genetic Technologies?: A Reassessment of the Evidence Suggests Not, 80 UMKC L. Rev. 563, 579-580 (2012); Price, *Unblocked Future: Why Gene Patents Won't Hinder Whole Genome Sequencing and Personalized Medicine*, 33 Cardozo L. Rev. 1601, 1618-1623 (2012). It is thus highly questionable whether Myriad's composition-of-matter claims would impede genetic testing.

3. Ostrer also exaggerates the effect of Myriad's claims by adopting a broad claim construction that directly contradicts the arguments he made in the district court. For example, Ostrer argues for the first time in this Court that Myriad's claims "reach any DNA if it is as little as 60% similar to the specified DNA" or "any DNA that creates proteins as little as 30% similar to the specified proteins." Pet. Br. 13. But in the district court, Ostrer and his expert witnesses argued that the portions of the specification he now cites do *not* alter the claims' plain meaning. *See* Grody Decl. ¶¶ 11, 14, 17, 26, 29 (Dkt. 67); Leonard Decl. ¶¶ 31, 34, 37, 46, 49 (Dkt. 68). Similarly, Ostrer now argues that the claims "reach all fragments of both the DNA and the proteins" and cover "other forms of genetic material," such as "'RNA.'" Pet. Br. 13. But in the district court, he argued that the claims do not cover anything more or less than the identified sequence. *See* AMP Summ. J. Br. 11 (Dkt. 62); Grody Decl. ¶ 29; Leonard Decl. ¶ 48. Other contradictions abound. *Compare* Pet. Br. 14 ("the sequence referenced is solely illustrative"), *with* AMP Summ. J. Br. 12 ("there is only one polynucleotide sequence that is covered by claim 2 and it is identified in the claim as SEQ ID NO:1").

These striking inconsistencies are not just technical errors. Rather, they go to the heart of Ostrer's strategy to exaggerate the impact of Myriad's composition-of-matter claims.

4. More generally, the claim that patents on isolated DNA molecules stifle basic research has no basis in fact. "[E]mpirical research suggests that the fears of widespread anticommons effects that block the use of upstream discoveries have largely not materialized." Caulfield et al., *Evidence and Anecdotes: An Analysis of Human Gene Patenting Controversies*, 24 Nature Biotech. 1091, 1093 (2006); *see also* Adelman & DeAngelis, *Patent Metrics*, 85 Tex. L. Rev. 1677, 1681 (2007) ("The existing empirical studies find few clear signs that the patenting of biotechnology inventions is adversely affecting biomedical innovation."). For example, a 2006 report by the National Research Council of the National Academies found that

> the number of projects abandoned or delayed as a result of technology access difficulties is reported to be small, as is the number of occasions in which investigators revise their protocols to avoid intellectual property complications or pay high costs to obtain access to intellectual property. Thus, for the time being, it appears that access to patents or information inputs into biomedical research rarely imposes a significant burden for academic biomedical researchers.

National Research Council, *Reaping the Benefits of Genomic and Proteomic Research* 134 (2006).

A 2005 survey of scientists involved in biomedical research found that "patenting does not seem to limit research activity significantly, particularly among those doing basic research." Walsh et al., *Patents, Material Transfers and Access to Research Inputs in Biomedical Research* 3 (2005). Only one percent of a random sample of 381 academic scientists reported a project delay of more than a month due to patents on materials necessary for their research, and none reported abandoning a research project due to the existence of patents. *Id.* at 17; *see also* Walsh et al., *View from the Bench,* 309 Science 2002 (2005).

An earlier study found that patents "rarely precluded the pursuit of worthwhile projects." Walsh et al., *Working Through the Patent Problem,* 299 Science 1021 (2003). It noted that "for a given project, usually fewer than a dozen outside patents require serious consideration, and the number of licenses required is much fewer, often none." *Id.* When requested, licenses were often available at minimal or no cost. Walsh, *Patents & Access,* at 17. "Thus, not only are barriers or delays rare, but costs of access for research purposes are negligible." *Id.*

Ostrer's arguments about stifling research also ignore the protection provided to researchers under 35 U.S.C. § 271(e)(1), *see Merck KGaA* v. *Integra Lifesciences I, Ltd.*, 545 U.S. 193 (2005), and the common law research exception, *see Whittemore* v. *Cutter*, 29 F. Cas. 1120, 1121 (C.C.D. Mass. 1813) (Story, J.). In addition, throughout the biotech industry, rational forbearance against researchers is the norm. *See, e.g.*, Chandrasekharan et al., *Propietary Science, Open Science and the Role of Patent Disclosure*, 27 Nature Biotech. 140, 140 (2009). This helps explains why "there is little documented evidence that patents covering genes or indeed any other subject matter have a detrimental impact on the conduct of research in the academic setting." Toneguzzo, *Impact of Gene Patents on the Development of Molecular Diagnostics*, 5 Expert Op. Med. Diagnostics 273, 274 (2011).

B. Patents On Isolated DNA Molecules Do Not Harm Patients

Ostrer's assertions about the effects of Myriad's composition-of-matter patents on patient health and access to medical care are also exaggerated. It is easy to argue after an invention has already been discovered and disclosed that the public would be better off if it were not patented. It is just as easy to single out a particular invention and argue with the benefit of hindsight that patent protection was not necessary for its discovery and development.

Such facile arguments ignore the long-term benefits that the public derives from providing patent protection in exchange for the disclosure of new and useful discoveries. *See, e.g., Eli Lilly & Co.* v. *Premo Pharm. Labs., Inc.*, 630 F.2d 120, 138 (3d Cir. 1980) ("Congress has determined that it is better for the nation in the long-run to afford the inventors of novel, useful, and nonobvious products short-term monopolies on such products[.]"). These arguments also ignore the fact that patent protection exists for a limited period, and once a patent expires, the invention enters the public domain. Indeed, Myriad's patents as well as many isolated DNA patents from the same era are due to expire in the very near future, after which the inventions will be in the public domain. *See* Resp. Br. 3

The advances made by the U.S. biotechnology industry under current law were not inevitable, and the industry's future success and continued global leadership depend on the ability to continue attracting private investors willing to shoulder the substantial risk of financing research and development. In the life sciences, early-stage companies hold roughly two-thirds of the future clinical pipeline. Boston Consulting Group, *Rising to the Productivity Challenge* 6 & ex. 4 (2004). Without patent protection for isolated DNA molecules, many companies would be unable to see those projects through to completion as potential sources of investment dry up. The list of potentially life-enhancing therapeutics and diagnostics that die in the pipeline as a result might never be known. But their absence would be acutely felt by patients suffering from the many diseases that currently lack effective treatments and cures.

C. The Biotechnology Industry Has Relied On The Patent Eligibility Of Isolated Compositions Derived From Nature

The Court must also weigh Ostrer's unsupported assertions against the reliance interests of an industry that depends on a stable patent system to sustain innovation. Any adverse effects that might result from the limited monopoly that a patent provides pale in comparison to the devastating impact Ostrer's proposed rule would have on the industry.

The United States tries to minimize the reliance interests at stake by noting that the PTO did not adopt its utility guidelines until 2001. *See* U.S. Br. 5, 27-28. But far more important than what the PTO has *said* is what the PTO has *done*. The PTO has been granting patents on isolated DNA molecules for thirty years and granting patents on other isolated compositions derived from nature for well over a hundred years. The United States also ignores the reliance fostered by decades of judicial precedent. *See* Resp. Br. 4-5 & n.2. The modern biotechnology industry has developed and flourished under this regime of consistent protection for isolated compositions derived from nature.

If a different balance is to be struck, it should be struck by Congress based on sound evidence and with due regard to the reliance interest of existing patentholders. *See Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002); *J.E.M. Ag Supply*, 534 U.S. at 145. In fact, Congress recently considered the issue of whether "gene patents" impede innovation or harm patients during its development of the America Invents Act, and opted to request a study on "effective ways to provide independent, confirming genetic diagnostic test activity where gene patents … exist." Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 27(a), 125 Stat. 284, 338 (2011). Once the PTO finishes the study and makes its required recommendations to the relevant House and Senate committees, Congress will have yet another opportunity to consider whether there is a need for targeted solutions in this area. Notably, Congress did *not* request an evaluation of whether "gene patents" themselves should be restricted or banned.

This Court should respect the broad language Congress chose to use in Section 101 and, with due regard for the reliance interests at stake, leave it to Congress to set policy in this area. To do otherwise would allow unsubstantiated assertions and exaggerations to upset decades of practice in a vast array of technological areas that are vital to human health.

CONCLUSION

For the reasons stated above, the judgment of the Federal Circuit should be affirmed.

Respectfully submitted.

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MARCH 2013

AMICUS
CURIAE
BRIEF

Supreme Court, U.S.
FILED
14 2013
OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE BOSTON PATENT LAW ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENTS

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THE BOSTON PATENT LAW ASSOCIATION'S INTEREST

The Boston Patent Law Association ("BPLA") is a nonprofit association of intellectual property attorneys and professionals who serve a broad range of clients that rely on the patent system, such as inventors, corporations, investors, universities, and research hospitals. These clients operate in an equally broad range of industries, including life sciences, high-tech, and traditional manufacturing.

The BPLA is concerned that denying patent eligibility to personalized medicine inventions, such as those at issue in this case, will hinder the development of better diagnostics and therapies, cripple the biotechnology industry, and discourage innovation generally.

Pursuant to F.R.A.P. 29(a), the BPLA has received the consent of all parties to file this *amicus* brief.[1]

SUMMARY OF ARGUMENT

This Court has posed the question for review as whether "human genes" constitute patent eligible subject matter within the meaning of 35 U.S.C. § 101. Congress, however, has already recognized that isolated human

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[1] This brief is solely the work of the BPLA and reflects its consensus view but not necessarily the view of any individual member or client. The BPLA's counsel in this matter contributed their time in preparing this brief *pro bono*. The BPLA funded all printing and other costs incurred in submitting this brief. No party or their counsel funded or prepared this brief in whole or in part nor made any financial contribution intended to fund this brief.

"genes" are patent eligible and, given the opportunity during the recent debate on patent reform, declined to exclude so-called "gene patents" from patent eligibility under § 101.

Further, the United States Patent and Trademark Office has, for at least the last three decades, issued "gene patents," and the biotechnology industry and others have come to rely on them. Thus, any sweeping contraction of the scope of patentable subject matter in this area, which would unsettle the expectations of the public based on thirty years of Patent Office practice, should be left to Congress, which has already initiated an investigation of the impact of the *Myriad* case and genetic testing patents in general.

Rather, this Court would provide a great service to the public by clarifying the legal principles underlying a §101 analysis as applied to biological products, including by reaffirming the approach of *Chakrabarty* and other cases requiring consideration of the claimed product as a whole and application of the pragmatic "new and useful" test to distinguish products of human ingenuity from products of nature. Indeed the Court could go a long way toward improving the clarity and stability of the law in this area simply by overruling the pre-1952 Act decisions in *Funk Bros.* and *Brogdex.* Those cases conflict with the *Chakrabarty* approach and were based on erroneous principles.

Finally the Court should avoid answering the question presented by the Petitioner—namely, "are human genes patentable?"--due to the inherent problems in the continually evolving, ambiguous conceptual term "gene." Answering this question, rather than a more proper question that focuses on the biochemical and structural terms used in actual patent claims, such as DNA structures or nucleic acid structures, will lead to confusion and ambiguity.

ARGUMENT

I. THIS COURT SHOULD DEFER TO CONGRESS'S RECOGNITION OF GENE PATENTS

The Leahy-Smith America Invents Act ("AIA") represented the most significant change to the United States patent system since 1952, aligning the U.S. with foreign patent jurisdictions by switching to a "first inventor to file" system and developing an expanded post-grant review procedure. In addition to these changes, Congress clarified the limits of § 101. Specifically, the U.S. Patent & Trademark ("USPTO") policy had been, and still is, that claims encompassing human organisms are patent ineligible. *See Manual of Patent Examining Procedure* ("MPEP") § 2105 (8th ed., Rev. 9, 2012). The USPTO, however, has for the last three decades issued "gene patents" claiming isolated nucleic acids or their use in diagnostic applications. *See* Eric J. Rogers, *Can You Patent Genes? Yes and No*, 93 J. Pat. & Trademark Off. Soc'y 19 (2010). As such, the USPTO did not consider that isolated genes constituted "human organisms" ineligible for patenting. Congress codified this USPTO policy and provided that any "claim directed to or encompassing a human organism" should be patent ineligible. *See* AIA § 33(a) (Pub. L. 112-29, § 33(a), 125 Stat. 284).

But that is as far as Congress went. In clarifying the limits of 35 U.S.C. § 101, Congress did not take the additional step of excluding isolated "genes," even though the question was certainly on everyone's mind. Indeed, the AIA was debated and enacted amidst ongoing controversy surrounding patents on isolated human "genes" and this *Myriad* litigation. In particular, Representative Dave Weldon, who proposed § 33(a), recognized that "the U.S. Patent Office has already issued patents on genes, . . . but it has not issued patents on claims directed to human organisms, including human embryos and fetuses. " 157 Cong. Rec. E1177-04 and 149 Cong. Rec. E2417-01.[2] Weldon further stated that his "amendment would not affect the former [patents on genes], but would simply affirm the latter." *Id.* In effect, Congress deferred to three decades of practice by the agency at the forefront of determining whether a patent application is directed to statutory subject matter, the USPTO. Thus, by recognizing the issue but declining to exclude genes when it clarified the scope of § 101, Congress effectively acknowledged that "genes" are patentable subject matter.

But Congressional involvement here is more than simply recognition. It has shown interest in the very subject matter at issue by requiring the USPTO to study the implications for health care of the whole category of patents of which the Myriad patent is a member--namely, genetic diagnostic testing patents. The study Congress has commissioned is a precursor to legislative fact-finding

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2. Representative Weldon's testimony was previously presented in connection with the Consolidated Appropriations Act, 204, Pub. L. No. 108-199, 634, 118 Stat. 3, 101, and later resubmitted with regard to the AIA.

and potential legislation in at least the narrower area of genetic testing and perhaps in the whole area of "gene patents."

Specifically, Congress mandated that the Director of the USPTO conduct a study "on effective ways to provide independent, confirming genetic diagnostic test activity where *gene patents* ... exist." AIA at § 27(a) (emphasis added). This study, which is now being conducted, requires an examination of "the effect that providing independent second opinion genetic diagnostic testing would have on the *existing patent* and license holders of an exclusive genetic test." *Id.* at §27(b) (emphasis added). In mandating this study, Congress signaled a desire to understand the commercial and healthcare issues associated with access to genetic testing, as raised in the *Myriad* litigation, and at the same time implicitly acknowledged the continued existence of gene patents that relate to such testing.

Under these circumstances, if a major change is to be made in patentable subject matter—potentially upsetting the expectations of the public after thirty years of isolated gene patenting—such change ought to be made by Congress, not this Court. This Court has said as much on more than one occasion and has declined to alter Congress's policy decisions regarding intellectual property laws. *See, e.g., Deepsouth Packing Co. v. Laitram Corp.*, 406 U.S. 518, 530 (1972) ("When Congress drafted § 271, it gave no indication that it desired to change either the law of combination patents as relevant here or the ruling of *Andrea*. Nor has it on any more recent occasion indicated that it wanted the patent privilege to run farther than it was understood to run for 35 years prior to the action of the Court of Appeals for the Fifth

Circuit"); *Sony Corp. v. Universal City Studios, Inc.*, 464 U.S. 417, 431 (1984) ("Sound policy, as well as history, supports our consistent deference to Congress when major technological innovations alter the market for copyrighted materials. . . . "). Thus, given the long period in which the USPTO and the public understood that the scope of patentable subject matter encompassed gene patents, if any change is to be made, it ought to be made by Congress.

But there is something this Court can and should do in deciding this appeal: take the opportunity to clarify the law regarding § 101 as it applies to products, the meaning of "manufacture" and "composition of matter" in § 101, and the product of nature doctrine. Confusion exists in this area, and a major reason for it is two precedents of this Court, *Funk Bros. v. Kalo* (1948) and *American Fruit Growers v. Brogdex* (1931), both decided before the 1952 Patent Act. As explained below, the BPLA urges this Court to overrule both cases so that the § 101 analysis will have the requisite logic, coherence, and practical wisdom of other relevant precedents, both from this Court and lower courts.

II. THE FACTS OF THIS CASE PROVIDE AN OPPORTUNITY TO CLARIFY WHEN BIOLOGICAL MATERIAL IS "NEW AND USEFUL" AND THUS PATENT ELIGIBLE UNDER §101

As argued below, the BPLA proposes an approach for evaluating § 101 eligibility in which the claimed biological product must be sufficiently different (new) from its natural state to confer a commercial, therapeutic, or diagnostic utility (use) not otherwise present absent the inventor's ingenuity. This simple approach will encourage innovation and avoid results that are based on ideology or misinformation rather than science, logical legal analysis, and sound public policy.

A. This Court Should Rely on the *Chakrabarty* Approach

In order to construe § 101 as it applies to biological products, this Court need go no further than to refer to its analysis and approach in *Diamond v. Chakrabarty,* 447 U.S. 303 (1980). In that case, this Court set out a two-part approach for evaluating the patent eligibility of claimed biological products: 1) view the claimed invention as a whole, and 2) determine whether the claimed invention as a whole is "new and useful" compared to what is in nature. *Id.* at 309-310. This approach will answer the ultimate question of whether the claimed product is a patent-eligible "manufacture" or "composition of matter," the very question answered by the Court in *Chakrabarty* with respect to the genetically engineered oil-consuming bacteria.

1. The Claimed Invention Should Be Analyzed as a Whole, Taking into Account the Inventive Human Concept behind It

As part of its eligibility analysis under § 101, the *Chakrabarty* court viewed the claim as a whole when it compared the claimed product, bacteria genetically engineered to consume oil, with bacteria in nature:

> His claim is not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring

> manufacture or composition of matter-a product of human ingenuity "having a distinctive name, character [and] use." . . .
>
> [t]he patentee has produced *a new bacterium* with markedly different characteristics *from any found in nature* and one having the potential for significant utility. His discovery is not nature's handiwork, but his own; accordingly it is patentable subject matter under § 101.

Id. 309-10 (emphasis added). Clearly this was a simple comparison between the claimed bacteria and the bacteria found in nature. There was no attempt to dissect the claimed product into the natural principles behind its creation and the application of those principles. It was also evident that the Court focused on the fact that a human conception ("ingenuity") lay behind the new product.

A year later, this Court reiterated that "[i]n determining the eligibility of respondents' claimed process for patent protection under § 101, their claims must be considered as a whole. It is inappropriate to dissect the claims into old and new elements . . . ." *Diamond v. Diehr,* 450 U.S. 175, 188 (1981) (emphasis added). The *Diehr* court then warned of the danger posed by dissection. Dissecting claims would "make all inventions unpatentable because all inventions can be reduced to underlying principles of nature which, once known, make their implementation obvious." *Id.* at 189, n. 12.

This Court again reaffirmed *Diehr*'s anti-dissection rule in *Bilski* and emphasized the need to consider the invention as a whole. *Bilski v. Kappos*, 130 S.Ct. 3218, 3230 (2010). Thus, when an invention relates to appreciation of a hitherto unappreciated natural principle, along with an insight that the natural principle can be applied, the appreciation of the natural principle and the application of it to a new and useful end must be considered as a whole--and not dissected into separate elements—when determining patent eligibility.

Although *Diehr* and *Bilski* involved process claims, the anti-dissection rule applies with equal force to product claims. All products are synthesized at some level from natural materials. If one were to dissect a product all the way to its natural components and the natural phenomena they embody, all products would become products of nature, and thus patent ineligible. Only when considering the invention as a whole can patent law encourage human ingenuity to utilize what is in nature and produce new and useful products from natural materials.

2. After Construing the Claim as a Whole, the Next Step Is to Ask Whether the Claimed Invention Is "New and Useful"

After considering the claimed subject matter as a whole, the *Chakrabarty* court determined that "[t]he patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility." *Chakrabarty*, 447 U.S. at 310. In essence the Court was applying the "new and useful" requirement of §101. The product was new because it did not exist in nature, and it had a utility that also did not exist in nature, *i.e.*, the capability of breaking down multiple components of crude oil. Such a product qualified as either a "manufacture" or a "composition of matter" under §101. *Id.* at 309.

The Court's "new and useful" test in *Chakrabarty* is straightforward and practical. It has many far-reaching benefits in encouraging innovation in the area of biological products. For example, resting patent eligibility on the "new and useful wording of § 101 leaves undisturbed historical patent protection for purified biological products such as vitamins, hormones, and antibiotics.

Chakrabarty, of course, was not the first time that a court focused on the "new and useful" requirement of §101 for eligibility. There is a rich history in the lower federal courts of the application of this test to uphold some of the most important pharmaceutical and biopharmaceutical inventions of the last hundred years.

For example, in 1911, as a district judge, Judge Learned Hand upheld the product claims of a patent directed to a form of adrenalin. *See Parke-Davis & Co. v. H. K. Mulford Co.*, 189 Fed. 95 (S.D.N.Y. 1911), *aff'd in pertinent part*, 196 Fed. 496 (2nd Cir. 1912). Although, the claimed compositions of matter had been isolated from the natural environment, Judge Hand found the difference between adrenalin in its natural environment and the claimed composition to be a distinction not in degree, but in kind, because the invention resulted in the product becoming available for public use:

> Nor is the patent only for a degree of purity, and therefore not for a new "composition of matter." As I have already shown, it does not include a salt, and no one had ever isolated a substance which was not in salt form, and which was anything like Takamine's. . . . That was a

> distinction not in degree, but in kind. But, even if it were merely an extracted product without change, there is no rule that such products are not patentable. Takamine was the first to make it available for any use by removing it from the other gland tissue in which it was found, and, while it is of course possible logically to call this a purification of the principle, *it became for every practical purpose a new thing commercially and therapeutically.* That was a good ground for a patent.

Id. at 103 (emphasis added).

Judge Hand drew the line between "different substances" and "degrees of the same substance" based on practical utilitarian advantages that would not have been enjoyed but for the inventor's contribution. *Id.* ("That the change here resulted in ample practical differences is fully proved. . . . The line between different substances and degrees of the same substance is to be drawn rather from the common usages of men than from nice considerations of dialectic").

Although Judge Hand's application of the "new and useful" test was implicit, a decision after enactment of the 1952 Act was explicit in relying on the "new and useful" requirement of § 101 when upholding the patent eligibility of vitamin B12 fermentation products. *Merck & Co., Inc. v. Olin Mathieson Chem. Corp.*, 253 F.2d 156 (4th Cir. 1958). Judge Haynsworth, writing for the Court of Appeals, put the product of nature doctrine in its proper context, foreshadowing the pragmatic view of this Court in *Diehr* on the role of nature in anything man-made:

> There is nothing in the language of the Act which precludes the issuance of a patent upon a 'product of nature' when it is a 'new and useful composition of matter' and there is compliance with the specified conditions for patentability. All of the tangible things with which man deals and for which patent protection is granted are products of nature in the sense that nature provides the basic source materials. The 'matter' of which patentable new and useful compositions are composed necessarily includes naturally existing elements and materials.

Id. 161-62.

In *Merck*, the claimed vitamin B(12) preparations were "beyond question . . . of very great therapeutic and commercial importance" *Id.* at 160. The court's comparison of the claimed products with nature was straightforward and practical. As it existed in nature, the product had no or very little therapeutic or commercial value and thus no utility. Only when converted into the claimed compositions did the product acquire such utility. *Id. at* 161. Indeed, the *Merck* court emphasized that nothing in nature compared to the claimed product:

> The compositions of the patent here have all of the novelty and utility required by the Act for patentability. They never existed before; there was nothing comparable to them. If we regard them as a purification of the active principle in natural fermentates, the natural fermentates are quite useless, while the patented compositions are of great medicinal

> and commercial value. The step from complete uselessness to great and perfected utility is a long one. That step is no mere advance in the degree of purity of a known product. *From the natural fermentates, which, for this purpose, were wholly useless and were not known to contain the desired activity in even the slightest degree, products of great therapeutic and commercial worth have been developed.* The new products are not the same as the old, but new and useful compositions entitled to the protection of the patent. . . . It did not exist in nature in the form in which the patentees produced it and was produced by them only after lengthy experiments.

Id. at 164 (emphasis added).[3]

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[3] *Merck* relied on *Parke-Davis* and also on two other cases that applied this "new and useful" approach to patentability. Both cases further support the proposition that patent eligibility can reside in making a substance therapeutically or commercially available to the public in a way that the natural form was not. *See Kuehmsted v. Farbenfabriken*, 179 Fed. 701, 705 (7th Cir. 1910) ("Hoffmann has produced a medicine [aspirin] indisputably beneficial to mankind--*something new in a useful art, such as our patent policy was intended to promote*. . . . though the difference between Hoffmann and Kraut be one of purification only--strictly marking the line, however, where the one is therapeutically available and the others were therapeutically unavailable--patentability would follow") (emphasis added) and *Union Carbide Co. v. American Carbide Co.*, 181 Fed. 106, 106-107 (2nd Cir. 1910) ("But patentable novelty in a case like the present may be founded upon superior efficiency; upon superior durability,. . . upon a lesser tendency to breakage and loss; upon purity, and, in connection with other things, upon comparative cheapness").

This "new and useful" approach thus presents a practical and clear way to determine whether a claimed biological product is patent-eligible as either a "manufacture" or a "composition of matter." But this test should not be confused with either the novelty requirement of 35 U.S.C. § 102 or the non-obviousness requirement of 35 U.S.C. § 103. The distinctiveness of these separate requirements is made clear by the wording of § 101 itself, which states that its requirements are "subject to the conditions and requirements of [Title 35]." The "new" requirement for biological products under § 101 is not with respect to the prior art but with respect to the corresponding product of nature, whether it was known or not.

B. *Funk Bros.* and *Brogdex* Cause Confusion and Should Not Factor into the Analysis Here

This Court's opinion in *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948), which was issued before the clarifying effect of the codification of the patent laws in 1952, is at odds with the anti-dissection approach of *Chakrabarty*, *Diehr*, and *Bilski*. This Court should thus overrule *Funk Bros.* to eliminate needless confusion in the application of § 101.

The *Funk Bros.* court erred by dissecting the claim to come to the wrong result about a new and useful product made by human intervention. The claimed product at issue in *Funk Brothers* was a package of combined mutually non-inhibitive strains of *Rhizobium* bacteria capable of inoculating different crops:

> An inoculant for leguminous plants comprising a plurality of selected mutually non-inhibitive strains of different species of bacteria of the genus Rhizobium, said strains being unaffected by each other in respect to their ability to fix nitrogen in the leguminous plant for which they are specific.

Id. at 128.

The majority opinion dissected the product claim into two elements: (1) the discovery of the fact that there are mutually non-inhibitive strains of *Rhizobium* bacteria; and (2) the application of this discovery to combine the selected strains into a single package capable of inoculating different crops. *Id.* at 131. The Court then held that the discovery of compatible strains is a discovery of "some of the handiwork of nature and hence is not patentable," and the application of that discovery is obvious because it is a simple packaging step. *Id.*

In light of *Chakrabarty*, *Diehr*, and *Bilski*, it is clear that the *Funk Brothers* court erred in dissecting the claim into the discovery element and the application element and then analyzing patent eligibility of each element separately. The Court then compounded this error by treating the discovery of the non-inhibitive property as if it were *prior art* to the application of it. Although referring to the discovery as part of the "storehouse of knowledge," in point of fact the mutually non-inhibitive property of certain strains had been *unknown* until the inventors discovered it. Essentially, the *Funk Brothers* majority required a non-obvious application of a hitherto unknown law of nature for a product claim to be patent-eligible, even when the discovery of the law of nature itself was part of the invention as a whole and itself "ingenious." *Id.* at 131.

The product claimed in *Funk Brothers* (*i.e.*, the combination of several previously unknown compatible strains) when considered as a whole was animated by a human conception of a new and useful product based on components that the art did not know existed--namely, the existence of compatible strains from different *Rhizobium* species. That conception, based on human ingenuity, led to selection and isolation of such hitherto unknown compatible strains and packing them into a single package, which was a new and useful human-made product markedly different from any then-known product. That product was "markedly different" from the prior art materials because there was no knowledge of the possibility of an effective package of mixed strains in the prior art due to the inhibiting effect. *Id.* at 129-130. Although the non-inhibitive strains may have performed the same function as the inhibiting ones, an effective package of mixed strains *did not exist in nature* before the invention and resulted from an inventive human conception. *Id.*

Further, that product, a single package of combined different strains, was "new and useful" because it allowed farmers to inoculate different crops with a single package of combined strains in a simple step and it helped the dealers and manufacturers to reduce inventories. Such a "new and useful" human-made product is not a product of nature, but a patent eligible "composition of matter" and "manufacture." The inventors were not being rewarded by a patent for the discovery of a law of nature but rather for the invention of a new and useful product.

It is important to recognize that *Funk Brothers* was decided before the requirement of non-obviousness was codified in section 35 U.S.C. § 103 in 1952. Although the general concept of obviousness had always been employed by the courts in deciding patent cases since at least *Hotchkiss v. Greenwood*, 52 U.S.(11 How.) 248 (1850), it was not as clear until 1952 that the obviousness analysis was distinct from a patent eligibility analysis. Understandably, the Court in *Funk Bros.* tended to confuse the two concepts. But since 1952 there have been two separate statutory provisions, § 101 for patent eligibility and § 103 for patentability based on nonobviousness. This Court in *Diehr* made clear that § 101 and § 103 require separate inquiries. 450 U.S. at 189-91.

Thus the Court in *Funk Bros.* had erroneously applied a dissection approach to the claim and then incorrectly combined a non-obviousness standard with the standard for patent eligibility when it incorrectly treated a hitherto unknown principle as prior art. Unless this Court overrules *Funk Bros.* as to its dissection approach, its conflation of eligibility and obviousness, and its result, it will continue to confuse the law of patent eligibility and specifically the product of nature doctrine.

Of course, it could be argued that *Diehr sub silentio* overruled *Funk Bros.* But because *Diehr* addressed process claims and *Funk Bros.* dealt with a product claim, it would be far better if this Court now expressly overruled *Funk Bros.* [4]

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[4] It is true that the Court in *Chakrabarty* did not overrule *Funk Bros.* but merely distinguished it. But if the Court in *Chakrabarty* had applied the same test to the claimed package

The other precedent of concern is *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1 (1931), which is based on a dubious analogy to tariff cases and thus, like *Funk Bros.*, should also be overruled. In *Brogdex*, this Court found that the product claim at issue, a borax-coated orange that is resistant to blue mold decay, was not a "manufacture" under the patent laws. That claim read as follows: "Fresh citrus fruit of which the rind or skin carries borax in amount that is very small but sufficient to render the fruit resistant to blue mold decay." *Id.* at 6. Under the approach outlined above, however, this Court would have reached a different result.

The *Brogdex* court started the patent eligibility analysis by asking whether the claimed subject matter was an article of manufacture. *Id.* at 11. The Court then relied on *Century Dictionary*'s definition of "manufacture":

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in *Funk Bros.* that it applied to Dr. Chakrabarty's bacteria, it could not have reached the same result as was reached in *Funk Bros.* The basis for the *Chakrabarty* distinction was the finding in *Funk Bros.* that the strains operated in the package the same way they operated in nature. But many patentable combinations involve components that operate in the combination the same way they have always operated alone. The *Funk Bros.* majority made the wrong comparison when it compared a component of the claimed combination with that component in nature. The comparison should have been of the claimed product *as a whole* with what was in nature. Based on that comparison, no such product existed in nature, and the claimed product produced a new and useful result. In terms of *Chakrabarty*, the package of different mutually non-inhibitive strains was "markedly different" from individual mutually non-inhibitive strains in nature and it provided "significant utility" to the vendor and the farmer.

> the production of articles for use from raw or prepared materials by giving to these materials *new forms, qualities, properties, or combinations*, whether by hand labor or by machinery; also anything made for use from raw or prepared materials.

Id. (*emphasis added*).

There is nothing wrong with that definition in determining whether the claimed product was an article of manufacture. But the Court then concluded that the claimed subject matter was not an article of manufacture and thus not patent eligible. *Id.* The Court reasoned that the addition of borax to the rind of an orange does not "produce from the raw material an article for use which possesses a new or distinctive form, quality, or property;" and that the product "remains a fresh orange, fit only for the same beneficial uses." *Id.*

That analysis was erroneous for at least four reasons. First, the use of borax to prevent blue mold decay of oranges was prompted by an inventive human conception, and the end product, a borax-coated orange, was made according to that inventive human concept.

Second, the claimed product was a human-made product markedly different from any natural product. The manufacturing process of such borax-coated oranges required immersion of fresh oranges in a solution of borax or boric acid and thus required human manipulation. The end product, a borax-coated orange, had a new property—resistance to blue mold decay—that natural oranges did not have.

Third, due to its new blue mold resistance, the borax-coated orange had new utilities, such as longer shelf life.

Fourth, the claimed product was a new combination of an orange and the chemical borax. The combination does not exist in nature but was artificially made. Therefore, the claimed product, a borax-coated orange, was a human-made product having new and useful qualities and properties and thus should have qualified as an article of "manufacture" under the *Century Dictionary*'s definition.

Nonetheless, the *Brogdex* court invalidated the claim, likely based on its reliance on the holdings of two tariff classification cases--*Hartranft v. Wiegmann*, 121 U.S. 609 (1887) and *Anheuser-Busch Brewing Ass'n v. United States*, 207 U.S. 556 (1908)--as guidelines for how to apply the definition of "manufacture" to the facts before it. There was nothing wrong with the Court's phrasing of the test used in the tariff cases when it concluded that "manufacture" requires transformation of raw material into a new and different article "having a distinctive name, character, or use." *Id.* at 12-13. Even under this definition, a borax-coated orange qualifies as an article of manufacture because it has a distinctive character and use compared to a natural orange, as discussed above. But the Court was strongly influenced by the holdings in the *Hartranft* and *Anheuser-Busch* cases that shellac-treated shells and treated corks were not "manufactures" for the purposes not of patent law but rather of tariff classifications.

The policy goals and purposes of patent law are quite different from those for tariff classifications. Patent law encourages human ingenuity, which is quite different from goods classifications for tariff purposes. The policy behind tariff regulation and classification is "to secure a just, impartial, and uniform appraisement of imported merchandise" and "assessment of duties thereon at the various ports of entry." 19 U.S.C. § 1502. Therefore, tariff classifications focus more on the nationwide and even global uniformity of classifications as promoting fairness in assessments rather than the actual accuracy of the classifications in an absolute sense. Determination of patent eligible subject matter under § 101, on the other hand, requires a focus on whether human inventive conception is responsible for a new and useful end product that does not exist in nature. The tariff classification cases cannot properly inform the meaning of patent eligible subject matter under § 101.

Mere structural difference between the raw material and the end product of manufacture should not be the focus of patent eligibility analysis under § 101. An article of manufacture should be *patent eligible* so long as there is an inventive human conception behind the manufacture that leads to a new and useful end product.

The *Brogdex* court stopped its patent eligibility analysis after the inquiry on the subject matter category of "manufacture" but failed to address another patent eligible category—"composition of matter." The claimed product, a borax-coated orange, is a combination of fresh orange and the chemical borax, and readily falls within the category of "composition of matter." So even on that basis, the *Brogdex* court should have reached a different conclusion. By relying on the factual holdings of tariff cases, *Brogdex* created a shaky foundation for understanding the laws on patent eligible subject matter.

Therefore, this Court should overrule *Brogdex* and dispel the confusion that it has caused and will otherwise continue to cause.

C. For Purposes of § 101, the Process Should Not Be Confused with the Product

Perhaps relying on this Court's opinion in *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012), Petitioner and its *amici* have conflated the process of making a product with patent claims directed to the product itself so as to confuse the § 101 analysis here. But the focus of a product claim should be on the product, viewed as a whole.

The conflation is two-fold. First, Petitioner and its *amici* have conflated the process used to make a product with the resulting product itself. The errant arguments are focused on the methods of producing isolated DNA and whether those methods amount to conventional or routine activity.[5] This is the wrong focus because it mixes apples (the process for making a product) with oranges (the separately claimed product itself). The process used for making a product, regardless of whether it is conventional, routine, or innovative, should not play a role in the determination of the patent eligibility of the product. The process for isolating DNA, while important for understanding the invention, should not be given weight in the analysis for patent eligibility.

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[5] Indeed, in his dissenting opinion below, Judge Bryson framed the question as "we are required to decide whether the process of isolating genetic material from a human DNA molecule makes the isolated genetic material a patentable invention." *Ass'n for Molecular Pathology v. U.S.P.T.O.*, 689 F.3d 1303, 1348 (Fed. Cir. 2012).

This Court has long considered the methods used for preparing a product as immaterial to the novelty or non-obviousness of a product. *See, e.g., General Electric Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 373 (1938) ("A patentee who does not distinguish his product from what is old except by reference, express or constructive, to the process by which he produced it, cannot secure a monopoly on the product by whatever means produced"). The lower courts have also held that the process for preparing a product is not relevant to its validity. *See, e.g., In re Pilkington*, 411 F.2d 1345, 1348 (C.C.P.A. 1969) ("Patentability of a claim to a product does not rest merely on a difference in the method by which that product is made. Rather, it is the product itself which must be new and unobvious"). Likewise, consideration of the process of manufacture must be kept out of the eligibility analysis for products under § 101 as well.

An analysis under § 101 that gives weight to the process for synthesizing a claimed product from a starting material can lead to inconsistent and absurd results. Simple processes that can be considered conventional or routine can transform products of nature into end-products with markedly different characteristics. There are numerous examples of transforming a natural product into a patentable, human-made product by applying simple steps such as mere application of heat. For example: (1) cracking of petroleum to produce acetylene and ethylene accomplished by mere application of heat[6]; (2) Curing natural rubber sap also accomplished by the application of heat.[7] An analysis that considers the process used in transforming natural products can render unpatentable many of the end products that have markedly different characteristics from natural products. An analysis that gives any weight to the process of converting the natural product to a different end product may incorrectly render transformed products unpatentable.

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[6] Green, MM. and Wittcoff, HA., *Organic Chemistry Principles and Industrial Practice*, 2003

Second, this "conventional or routine activity" approach is taken out of context from *Prometheus*, which, as applied by Petitioner, appears to dissect the process claim at issue there into its component parts. But a closer reading of *Prometheus* shows that it has not resurrected the incorrect dissection analysis of *Funk Bros.* in its approach to the process claims there. The representative claim ended in a "wherein" clause that plainly was a statement of the law of nature. *Id.* It is not dissection to look at a claim and point out that all that it is doing is telling physicians to use that law. On the other hand, *Funk Bros.* clearly applied a dissection approach when it struck down a new and useful product nowhere found in nature. Further, *Prometheus* cites *Diehr* for the proposition that a court must view the claimed subject matter as a whole when analyzing validity under § 102 or § 103. That proposition is, of course, correct. But *Prometheus* overlooked the fact that in declaring this rule, *Diehr* was specifically referring to § 101, not § § 102 or 103.

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[7] Curing rubber and cracking petroleum have been important subjects of litigation in several cases before this Court: *See Diamond v. Diehr*, 450 U.S. 175 (1980); *Universal Oil Products Co. v. Globe Oil & Refining Co.*, 322 U.S. 471 (1944); *Corona Cord Tire Co. v. Dovan Chemical Corp.*, 276 U.S. 358 (1928); *Sinclair Refining Co. v. Jenkins Petroleum Process Co.*, 289 U.S. 689 (1933); *Standard Oil Co. v. United States*, 283 U.S. 163 (1931).

The § 101 ineligibility of the *Prometheus* claims was that they were simply statements of a natural correlation with an admonition to apply it. *See Prometheus*, 132 S. Ct. at 1297-98. But this analysis has no bearing on the analysis of biological products. Unlike process claims, which are a series of steps, a product claim is a tangible thing. It cannot be a statement of anything. The questions under § 101 for such a product are quite practical—can the claimed product, viewed as a whole, be found in nature, and is the claimed product new and useful in a way that the products of nature are not.

Product claims cover tangible substances and do not pose the difficulties associated with process claims in comparing them with a product of nature for patent eligibility. While the process claims from the long line of cases considered by this Court involved the difficult separation of laws of nature from the additional process steps, the products represent tangible substances that can be directly compared with a product of nature. The difficulty in analyzing process claims and separating a natural law or principle from the process claim has been well recognized by this Court. In contrast, compositions, manufactures, and machines are tangible, observable things which can be easily compared. "A machine is a thing. A process is an act, or a mode of acting. The one is visible to the eye, -- an object of perpetual observation. The other is a conception of the mind, seen only by its effects when being executed or performed." *Tilghman v. Proctor* 102 U.S. 707, 728 (1880). Similar to claims involving machines, the product claims represent tangible things, visible in the aggregate, and observable in the structural level through well-established techniques.

This Court has long recognized the difficulties in separating the law of nature from the process embodying it. "The line between a patentable "process" and an unpatentable "principle" is not always clear. Both are "[conceptions] of the mind, seen only by [their] effects when being executed or performed." *Parker v. Flook*, 437 U.S. 584, 589 (1978) (citation omitted). A product on the other hand is directed to visible, observable things that can be compared to a product of nature to determine the differences in their character, name, and use. The Court should thus affirm the standard for patent eligibility for products outlined in *Chakrabarty*, holding that a product that is different from the natural product (*e.g.*, by having a significant utility not present in the natural product) is patent eligible. 447 U.S. 303, 309-10.

III. THE MEANING OF "GENES" IS AMBIGUOUS AND THUS A DECISION THAT SIMPLY REFERS TO PATENT ELIGIBILITY OF "GENES" WILL BE UNCLEAR

The BPLA has, to this point, discussed what it believes are the correct legal principles underlying the §101 analysis. The remaining challenge is framing the question properly. As framed by Petitioner, the question for this appeal is "Are human genes patentable?" This question, however, should not be answered because, even with the legal principles clarified, it will lead to confusion and overly broad rulings that do not take into account the different concepts that can be encompassed by the word "gene." Because claims and claims alone define a patented invention, the BPLA suggests that the question be rephrased in terms that will keep the focus on the invention *as claimed*, by using words that are actually found in patent claims, such as DNA structures or nucleic acid structures--terms that describe actual biochemical materials, not vague, continually changing concepts such as "genes."

A. A "Gene" Is a Concept; DNA Is a Molecule

To frame the question properly, one must first define "gene." The concept has evolved with time, from functional to chemical and back to functional again.[8] Indeed, the word "gene" is used differently by scientists, policy researchers, and science writers. For example, the term "gene" may encompass the concept of a unit of information or instructions, as specified by a sequence of nucleotides. The term "gene" may encompass a naturally occurring nucleic acid molecule or set of nucleic acid molecules that interact(s) with other naturally occurring molecules, *e.g.*, proteins, in coordinated ways in a cell to produce proteins and other nucleic acids that are important to the life of the cell or organism within which the cell resides. The term "gene" may encompass a nucleic acid molecule or set of nucleic acid molecules that have been isolated from their natural context and that take on one or more new structural or functional properties in isolation from their natural environment. The term "gene" may encompass a synthetic nucleic acid molecule (*e.g.*, chemically synthesized under controlled chemical conditions engineered by humans), which may or may not represent a naturally occurring nucleic acid molecule. It is not surprising that the general public and even those skilled in the art are not clear on the concept.

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[8] *See* Gerstein, M.B., et. al.. *What is a gene, post-ENCODE? History and updated definition*, 2007 Genome Res. 17, 660-681 (also available at http://genome.cshlp.org/content/17/6/669.full, last visited March 13, 2013).

A 1909 definition of "gene," predating the discovery of the double helix molecular structure for deoxyribonucleic acid "DNA" by nearly fifty years, relies on functional, not chemical language. For example, Wilhelm Johannsen, the Danish botanist who coined the term, defined "gene" as "special conditions, foundations and determiners which are present [in gametes] in unique, separate and thereby independent ways [by which] many characteristics of the organism are specified." Johannsen, W., *Elemente der exakten Erblichkeitslehrek*, Jena. 124 (1909), *quoted in* Nils Roll-Hansen, *The Crucial Experiment of Wilhelm Johannsen*, 4 Biol. Philos. 303, 303-329 (1989).

Once the DNA molecule was characterized, definitions moved to the realm of chemistry. For example, *The Random House Dictionary of the English Language*, (2d ed., 1987) defines "gene" as "the basic linear unit of heredity; a linear sequence of nucleotides along a segment of DNA that provides the coded instructions for synthesis of RNA, which, when translated into protein, leads to the expression of hereditary character."

Since then, it has become clear that the protein coding regions in humans are not "linear units." The protein coding regions, called exons, are separated by non-protein coding regions, called introns. The exons are not all in a line with the introns that separate them, or even necessarily close to one another. Researchers were surprised by the sheer quantity of non-protein coding introns ("junk DNA") relative to protein coding exons because only about one percent of the DNA appeared to code for protein. *See* Lander, E.S., *et al., Initial sequencing and analysis of the human genome*. 409 Nature 860, 860–921 (2001). *See also* J. Craig Venter *et al., The sequence of the human* *genome*, 291 Science 1304, 1304-1351 (2001). Now scientists are discovering that the so-called "junk DNA" may affect the operation of the exons, further confusing the meaning of "gene." *See* Gina Kolata, *Bits of Mystery DNA, Far From 'Junk,' Play Crucial Role*, New York Times (Sept. 5, 2012) (available at http://www.nytimes.com/2012/09/06/science/far-from-junk-dna-dark-matter-proves-crucial-to-health.html?pagewanted=all&_r=0, last visited on March 13, 2013).

Nearly one hundred years after Johannsen, Gerstein *et al.*, in their paper entitled "What is a gene, post-ENCODE? History and an updated definition," propose a return to defining "gene" by reference to a function:

> A gene is a union of genomic sequences encoding a coherent set of potentially overlapping functional products. Our definition side steps the complexities of regulation and transcription by removing the former altogether from the definition and arguing that final, functional gene products (rather than intermediate transcripts) should be used to group together entities associated with a single gene. It also manifests how integral the concept of biological function is in defining genes.

Mark B. Gerstein, *et al. What is a Gene Post-Encode? History and Updated Definition*, 17 Genome Res. 660, 660 (2007). Thus, "gene" is an evolving concept.

Deoxyribonucleic acid ("DNA"), on the other hand, is a tangible molecule. Petitioners have conflated the biochemical and quotidian meanings of DNA, elevating its status, and then assigned it to an out of date understanding of "gene." The Court must not rule on a concept, namely, a "gene," which is evolving with every experiment. The Court should be mindful, as are biologists working on the ENCODE Project Consortium and the International Human Epigenome Consortium, that DNA *in vitro* (*i.e.*, engineered or isolated into a useful form) is not and does not behave like DNA *in vivo*. See The Encode Project Consortium, *An Integrated Encyclopedia of DNA Elements in the Human Genome*, 489 Nature 57, 57-74 (2012). This understanding will free the Court to consider the patent eligibility of various aspects of isolated DNA on their merits.

B. The Term "Gene Patents" Is Likewise Unclear

As described above, the definition of genes has evolved greatly over the past century. It is not surprising, therefore, that a definition of "gene patent" is elusive. Indeed, "gene patents are the subject of considerable debate and yet, like the term 'gene' itself, the definition of what constitutes a gene patent is fuzzy." Kyle Jensen and Fiona Murray, *Intellectual Property Landscape of the Human Genome*, Science, 310, 239 (2005).

In February 2012, and pursuant to its charge under the AIA to investigate the commercial and healthcare implications of "gene patents," the USPTO held a public hearing on genetic diagnostic testing. During this hearing, one commentator, Thomas Kowalski, pointed out that patent law lacks a clear definition of the term "gene patent":

> On the lack of definitions, is a gene patent supposed to be those patents that claim isolated nucleic acid molecules or only isolated DNA? That is, for example what about claims to RNA? The Manual of Patent Examining Procedure, MPEP, is a guide for examiners. In Section 2163, the MPEP states that a gene comprising SEQ ID No. 1 requires a determination of what the claim covers as a whole, and a conclusion that specific structures such as a promoter, a coding region, or other elements are included. In other words, the term "gene" contains more than merely sequences that encode a protein.
>
> For example, a gene can contain a promoter region, a region of DNA that facilitates transcription of a coding region. There are patent claims to promoters. Are these gene patents? Also, there is DNA encoding what is known as a leader sequence or a signal sequence that is an extension of a protein that facilitates transport of a protein out of a cell and is cleaved from the protein. There are patent claims to signal sequences or leader sequences. Are these gene patents?
>
> The term "gene patents," to me, is unclear…

http://www.uspto.gov/aia_implementation/120216genetic_transcript.pdf

The Court should thus adjudicate without the confusing use of the term "gene patent," focusing instead on what is actually claimed, such as isolated DNA and other molecules.

C. The Court's Analysis Should Not Be Directed to "Genes" but Rather To Useful Nucleic Acids or DNA

As illustrated above, the term "gene" is an imprecise term that encompasses different aspects. But strong arguments can be made that, if by a "gene" one means "a nucleic acid isolated from its natural environment" (e.g., removed from a cell, excised from a chromosome, and/or placed in a vector), then such a nucleic acid could meet the "new" prong of the "new and useful" requirement, to the extent that it is a composition produced through human intervention.

Isolated DNA is not only new (*i.e.*, different from the native DNA) but also *"markedly different"* if its differences are sufficient to confer on it a practical commercial, therapeutic, or diagnostic utility or advantage that is not otherwise present in the unadulterated, or native, state. Such an isolated DNA would be characterized as "markedly different" because it would have distinctive name, character, and use.

By way of example, isolated DNA produced synthetically as primers may be reacted under controlled conditions with polymerase enzymes to generate millions of copies of nucleic acids from a single template nucleic acid. This DNA amplification technology – referred to as polymerase chain reaction – relies on such isolated DNAs and has a broad range of commercial uses, including in DNA sequencing for diagnostics and basic research, genetic fingerprinting (for forensic sciences, paternity testing, pathogen detection, etc.), creating constructs for gene therapy, and other areas. Under the test posed in Section II above, therefore, this product would be patent eligible.

Thus, consistent with the 'new and useful' test proposed above, strong arguments can be made for patent eligibility of a nucleic acid molecule that is chemically synthesized (*e.g.*, a full length nucleic acid or synthetic probes or primers), amplified in a test tube (for example by PCR or other *in vitro* amplification technique involving human engineering), or amplified in a cell (for example in a vector or other cellular amplification technique involving human engineering), even if it has a specific naturally occurring nucleotide sequence--if the nucleic acid molecule is useful in a way that the naturally occurring molecule was not.

CONCLUSION

For the reasons detailed above, the Boston Patent Law Association respectfully submits that this Court should defer to Congress and rule in a manner that is consistent with the 'new and useful' standard as discussed herein, taking the opportunity to clarify the proper approach for analyzing the patentability of biologic products under the "new and useful" test. Finally, because of the ambiguity in the meaning of "genes," and therefore "gene patents," a decision that simply refers to patent eligibility of "genes" would be unintentionally broad sweeping and might effectively disqualify many worthy patentable inventions and forestall development of many worthy biological products. The Court should resist the call to make an overarching and unintentionally broad pronouncement on "gene patents" because the term itself is ambiguous and will lead to further confusion.

March 14, 2013

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AMICUS
CURIAE
BRIEF

RECORD AND BRIEFS

Supreme Court, U.S.
FILED
JAN 31 2013
OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR
MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

On Writ of Certiorari to the United States Court of
Appeals for the Federal Circuit

BRIEF FOR CANAVAN FOUNDATION, CLAIRE ALTMAN HEINE FOUNDATION, MARCH OF DIMES FOUNDATION, FACING OUR RISK OF CANCER EMPOWERED, NATIONAL ASSOCIATION FOR PSEUDOXANTHOMA ELASTICUM, AND OVARIAN CANCER NATIONAL ALLIANCE AS *AMICI CURIAE* IN SUPPORT OF PETITIONERS

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Stifling or Stimulating – The Role of Gene Patents in Research and Genetic Testing: Hearing Before the Subcomm. on Courts, the Internet and Intellectual Property of the H. Comm. on the Judiciary, 110th Congress 35 (2007) 14

Tom Walsh et al., *Spectrum of Mutations in BRCA1, BRCA2, CHEK2, and TP53 in Families at High Risk of Breast Cancer*, 295 J. Am. Med. Ass'n 1379 (2006) 10, 11

U.S. DEP'T OF HEALTH & HUMAN SRVS., SECRETARY'S ADVISORY COMMITTEE ON GENETICS, HEALTH, & SOCIETY, GENE PATENTS AND LICENSING PRACTICES AND THEIR IMPACT ON ACCESS TO GENETIC TESTS (2010) 12, 13

STATEMENT OF INTEREST OF *AMICI CURIAE*[1]

Each of the groups who submit this amicus brief represents a population of patients and their families who are adversely affected by the practice of patenting human DNA. Patents like Myriad's raise testing costs and simultaneously impede the development of more accurate and reliable diagnostic tools. The results are concretely and tragically experienced by patients and their families whose suffering might have been minimized or prevented altogether by more effective and less expensive means of testing for the genetic disposition to certain life threatening diseases.

Canavan Foundation is a non-profit organization with the mission to provide funding for research efforts to find an effective therapy for, raise awareness of, and to help avoid Canavan disease through carrier screening and prenatal testing. Despite efforts to sponsor low cost screening for potential carriers of Canavan disease, a doctor and hospital who patented the relevant gene have prevented the group's efforts to provide free or inexpensive screening programs.

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[1] No counsel for a party authored this brief in whole or in part, and no such counsel or a party made a monetary contribution intended to fund the preparation or submission of this brief. No party or entity other than amici, their members, or their counsel, made a monetary contribution to this brief's preparation or submission. Petitioners have filed a letter with the Clerk of the Court granting consent to the filing of any and all amicus curiae briefs. Respondents' letter granting amici consent to file has been filed with the Clerk of the Court.

Claire Altman Heine Foundation (CAHF) is a non-profit organization dedicated to establishing pan-ethnic carrier screening for Spinal Muscular Atrophy (SMA)—the number one genetic killer of children under two. In CAHF's experience, the use of patent rights relating to the gene responsible for SMA has reduced access to SMA carrier screening.

Facing Our Risk of Cancer Empowered (FORCE) is a non-profit organization whose mission includes providing people with information and resources to determine whether they are at high risk for breast and ovarian cancer due to family history or genetic predisposition.

March of Dimes Foundation is a non-profit organization dedicated to improving the health of babies by preventing birth defects, premature birth and infant mortality. The March of Dimes Foundation has been in the forefront of supporting research on the genetic factors in diseases and the best methods of testing and treatment. March of Dimes' mission and research are adversely affected by patents on gene sequences.

National Association for Pseudoxanthoma Elasticum (NAPE) is a non-profit organization and the original Pseudoxanthoma Elasticum (PXE) patient support group in the United States, committed to providing education for afflicted individuals and families. NAPE opposes gene patents because they interfere with research and development of diagnostic and therapeutic tools.

Ovarian Cancer National Alliance (OCNA) is a non-profit organization and the foremost advocate for women with ovarian cancer in the United States. OCNA opposes gene patents because such monopolies impede research on ovarian cancer and restrict access to genetic testing for the disease.

SUMMARY OF THE ARGUMENT

The issue before the Court is whether human genetic material, or a segment of the human genome, upon isolation and/or extraction from the body, constitutes patent eligible subject matter as defined in 35 U.S.C. § 101 . To be clear, the patents now at issue do not claim a means of isolating or extracting the gene; they claim the gene itself as invention. The U.S. District Court held that the genes as defined in the patent claims are "products of nature" and fall squarely within the judicially recognized exceptions to patentable subject matter. On appeal, the Federal Circuit panel affirmed the lower court's invalidation of all but one of Myriad's method claims but reversed its invalidation of composition claims, holding that the genetic sequences themselves were patent eligible. The panel was divided and produced three separate opinions, including one concurrence and one dissent. Writing for the majority, Judge Lourie concluded that the mere *isolation* of a gene sequence was alone sufficient to qualify the genetic material as a product of human invention, despite the fact that the nucleotide sequence of the gene had not been altered, added to, reduced, or manipulated in any way.

On Plaintiffs' first Petition, this Court issued an order granting certiorari, vacating the Federal Circuit's decision and remanding this case to the

Federal Circuit for further proceedings in light of this Court's decision in *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012). On remand, the same Federal Circuit panel affirmed its previous decision and issued a new set of opinions that are substantially the same as those issued previously. This result was unsurprising in view of the fact that the majority declared this Court's *Mayo* decision categorically irrelevant to composition of matter claims at issue in *Myriad*. According to the Federal Circuit's majority opinion, "*Mayo* does not control the question of patent-eligibility of such claims. They are claims to compositions of matter, expressly authorized as suitable patent-eligible subject matter in § 101." *Association for Molecular Pathology v. USPTO*, 689 F.3d 1303, 1325 (Fed. Cir. 2012). "[A] composition of matter is not a law of nature." *Id.* at 1331.

Petitioners again sought review by this Court, and on November 30, 2012, this Court granted petition for review on the single issue of whether human genes are patentable. Petitioners timely filed their brief in support of the district court's holding that human genetic sequences are not patentable subject matter. The Amici described herein now file their brief in support of petitioners.

Gene patents create a monopoly over information that is foundational for the biological and medical sciences. By authorizing such monopolies, the Federal Circuit's decision sets a precedent that impedes research and innovation in the natural sciences. It is therefore inimical to the goals of innovation and growth for which the U.S. patent laws were designed.

In addition to its deviation from this Court's jurisprudence on fundamental issues affecting the scope and purpose of patent law, the Federal Circuit's decision authorizes patent practices that will severely compromise efforts in the U.S. to diagnose and treat chronic and life-threatening diseases. The adverse effects of gene patents on science and healthcare are profound and wide ranging.

As the patient groups who submit this brief are keenly aware, the Federal Circuit's decision not only subverts the constitutionally grounded purposes of the patent laws but ushers in a set of commercial practices that are injurious to the health and welfare of U.S. citizens. For these reasons, we urge the Court to reverse the Federal Circuit's decision and to uphold the decision of the district court below, finding that human genetic material is not patent eligible subject matter under § 101 of the U.S. Patent Act.

ARGUMENT

I. GENE PATENTS AFFORD A PRIVATE MONOPOLY OVER THE BASIC TOOLS AND SOURCES OF SCIENTIFIC KNOWLEDGE AND THEREBY UNDERMINE THE GOALS OF INNOVATION AND EXCHANGE FOR WHICH THE U.S. PATENT LAWS WERE DESIGNED

As this Court recognized in *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012), the scope of patent-eligible subject matter is not limitless but instead reflects a balance of values. The patent offers a limited monopoly in exchange for information and does so to encourage innovation in the arts and sciences for the public good. The courts have recognized that just as insufficient patent protection fails to incentivize, too much patent protection obstructs the exchange of information necessary for innovation. Hence, for over 150 years, courts have disallowed patent claims that impede future innovation by preempting or broadly covering natural phenomena or natural laws: "The Court has repeatedly emphasized ... a concern that patent law not inhibit further discovery by improperly tying up the future use of laws of nature." *Id.* at 1301; *see O'Reilly v. Morse*, 56 U.S. (15 How.) 62, 112-20 (1854).

Patents on natural phenomena undermine the patent system by allowing the patent holder to control any and all uses of the claimed phenomena. The obstructive effects of patents that preempt natural laws were recognized early on in *Morse*, where the Court considered a series of claims for the use of electromagnetic force. *Id.* While upholding the validity of Morse's claims directed to specific applications, the Court invalidated Morse's eighth claim which broadly covered *any* use of electromagnetic force "for making or printing intelligible characters, signs or letters at a distance." *Id.* at 112. In rejecting this claim the Court explained:

> And if he can secure the exclusive use by his present patent he may vary it with every new discovery and development of the science, and need place no description of the new manner, process, or machinery, upon the records of the patent office ... he claims an exclusive right to use a manner and process which he has not described and indeed had not invented, and therefore could not describe when he obtained his patent.

Morse, 56 U.S. at 113. Morse's eighth claim was found to be so broad that it would cover virtually every use of electromagnetism for printed communication. The claim would have tied up a field of basic knowledge and prevented others from using it to make valuable contributions. Patent claims on human genetic sequences have had the same effect in the medical sciences. Myriad's patents have allowed it to stifle and/or control a huge amount of data on the nature and significance of variants in the BRCA1 and BRCA2 genes. Myriad has no reason to identify or disclose additional variations in the BRCA1 and BRCA2 genes when they have patent claims covering practically all variations thereof. *See e.g.*, Myriad's Patent No. 5,837,492, claim 6 (covering mutations of a BRCA2 polypeptide which correlate with an increased risk of cancer); Myriad's Patent No. 5,747,282, claims 5 and 6 (covering DNA sequences with "at least 15 nucleotides" of an identified sequence). The vast data that Myriad does collect from its testing, it has refused to disclose with the scientific community. Andrew Pollack, *Despite Gene Patent Victory, Myriad Genetics Faces Challenges*, N.Y. Times, Aug. 24, 2011.

Advocates of gene patenting, such as Myriad, argue that prohibiting gene patents would impede innovation and compromise medical diagnosis and treatment. But there is no factual support for those assertions. To the contrary, unless the Federal Circuit's decision is reversed, the result will be less research, inferior diagnostic testing, and worse outcomes for patients. The negative impact of gene patents on medical research, diagnostic procedures, and patient outcomes is no longer speculative; there is ample empirical evidence of their detrimental effects.

A. *Specific Consequences of Myriad's Patents*

As a consequence of its patents, Myriad gained the exclusive right to perform genetic testing and research on the BRCA1 and BRCA2 genes in the United States. When one party such as Myriad controls all testing of a gene sequence, it has no incentive to develop further knowledge of gene mutations affecting the risk of breast cancer or improve the quality of testing. Indeed there are multiple scientific studies that demonstrate the significant limitations of Myriad's test.[2] According to one study published in 2006, the test Myriad employs to detect breast cancer risk does not take into account significant possible mutations of the gene that correlate with a susceptibility to breast cancer. Tom Walsh et al., *Spectrum of Mutations in BRCA1, BRCA2, CHEK2, and TP53 in Families at High Risk of Breast Cancer*, 295 J. Am. Med. Ass'n 1379, 1379-1388 (2006). In the study, researchers sampled DNA from 300 members of high-risk families that had received negative test results from Myriad. *Id.* The researchers used six methods to search DNA for breast cancer gene mutations, and found that 12% of the patients studied carried rearrangements of BRCA1 or BRCA2 that were not included in Myriad's array. *Id.*[3] Despite this and other empirical evidence that Myriad's test is deficient and often produces ambiguous results even with the mutations it checks, Myriad, as a result of its DNA sequence patents, remains in sole control of how or whether any new research on the BRCA genes will be conducted and/or incorporated into the tests that it offers.

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[2] *See* Maurizia Dalla Palma et al., *The Relative Contribution of Point Mutations and Genomic Rearrangements in BRCA1 and BRCA2 in High-Risk Breast Cancer Families*, 68 Cancer Research 7006, 7011 (2008) (finding 8% of non-Ashkenazi Jewish test subjects carried a BRCA mutation not detectable by Myriad's standard test); Allison W. Kurian et al., *Performance of BRCA1/2 Mutation Prediction Models in Asian Americans*, 26 J. Clinical Oncology 4752, 4754-56 (2008) (finding that the models used by Myriad underestimate the prevalence of BRCA1/2 mutations among Asian American women by a full 50%).

Furthermore, Myriad's patent monopoly severely restricts the availability of second opinions from medical experts. Although Myriad argues that multiple laboratories provide second opinions for BRCA1 and BRCA1 test results (Myriad Brief in Opposition to Petition for Writ of Certiorari at 16 (S. Ct. Oct. 31, 2012)), these laboratories use the same exclusive test offered by Myriad. The only available option for a woman seeking a second opinion is the same test, which will not find mistakes inherent in the test, such as the exclusion of cancer causing mutations in the testing protocol.

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[3] The number of missed mutations may be even higher. According to Institute Curie geneticist Dr. Dominique Stoppa-Lyonett, Myriad's test may miss up to 20% of the expected BRCA1 mutations. Steve Benowitz, *French Challenge to BRCA1 Patent Underlies European Discontent*, 94 J. Nat'l Cancer Inst. 80, 80 (2002).

B. *Adverse Effects of Gene Patenting Generally*

Myriad's patents provide but one example of the adverse effects of patents that preempt natural phenomena. In April 2010, the U.S. Department of Health and Human Services issued the Secretary [of Health and Human Services]'s Advisory Committee on Genetics, Health, and Society, Report on Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests (2010) [hereinafter "SACGHS"]. The SACGHS report found that research in the field of genetics has already begun to suffer as a consequence of gene patents. "Patents are already hindering the development of multiplex tests. Laboratories utilizing multiplex tests are already choosing not to report medically significant results that pertain to patented genes for fear of liability." *Id.* at 3. As a consequence of their chilling effects on genetic research, the existence and enforcement of gene patents discourage the development of better quality testing methods. "Neither sample sharing nor competition is possible when an exclusive-rights holder prevents others providing testing. As a result, significant concerns about the quality of a genetic test arise when it is provided by a patent-protected sole provider." *Id.* at 4.

Perhaps most directly and immediately of concern to the groups who submit this brief, the practice of patenting human genetic material has already proven to increase the costs of diagnostic procedures, restrict patient access to existing genetic testing, and preclude the availability of better tests and of second opinions of the often ambiguous results of current testing methods. *See Id.* at 1-6.

C. *Salient Cases of Individual Hardship Attributable to Genetic Patents*

There can be no doubt that patents on human genes worsen patient outcomes. The harm that results from patenting human genes is dramatically illustrated in the case of a young girl named Abigail who lost her life to a disease called familial Long QT syndrome (LQTS). LQTS is a disorder of the heart's electrical system that affects 1 in 3,000 newborns and can result in sudden death. Misha Angrist, et al, *Impact of Patents and Licensing Practices on Access to Genetic Testing for Long QT Syndrome*, SACGHS at Appendix A, F-1. The disease has been correlated to mutations within three particular genetic sequences. The company that obtained a patent and exclusive license to the mutated genes developed a diagnostic test, but did not offer it for two years because the exclusively-licensed laboratory went into bankruptcy. During that time, the company nevertheless sought to enforce the patent against other parties who could have provided genetic testing for LQTS. *Stifling or Stimulating – The Role of Gene Patents in Research and Genetic Testing: Hearing Before the Subcomm. on Courts, the Internet and Intellectual Property of the H. Comm. on the Judiciary*, 110th Congress 35, 40

(2007) (statement of Dr. Marc Grodman). In the case of at least one patient, a ten year-old girl named Abigail who presented with an arrhythmia, death was preventable. *Id.* If the patent holder had made testing available, the cause of Abigail's arrhythmia would have been readily identified as LQTS, and the appropriate therapies (beta-blocker drugs, implantable cardioverter-defibrillators, and avoidance of certain arrhythmia triggers) could have been prescribed. *Id.*; Angrist, SACGHS at Appendix A, F-1.

In addition to such adverse effects on the availability and affordability of quality testing, individual patients and their families have been abused by physicians and hospitals who are incentivized to patent genes for commercial gain. No case illustrates this problem better than the history of the discovery of genetic factors for Canavan disease. Beginning in the early 1990s, Ashkenazi Jewish families of children with Canavan disease provided tissue and money for over a decade to a research physician so that he could sequence the genetic mutation that caused this devastating neurological disease. The Greenbergs—whose two children were afflicted with and died from Canavan disease—rallied other Canavan's families and together they freely gave blood and tissue samples from their dying children. Their purpose was to provide a low cost screening and prenatal testing program to identify potential carriers of the disease. Soon after the research physician (a long-time personal physician of the Greenbergs) identified the relevant gene sequence for carriers of the mutation, he and his hospital patented it without the knowledge or consent of the tissue sources. *See Greenberg v. Miami Children's Hosp. Research Inst., Inc.*, 264 F. Supp. 2d 1064 (S.D. Fla. 2003). When the Canavan Foundation and its constituents convinced medical providers to offer Canavan gene testing for free, the hospital threatened to enforce its patents and shut down the free testing.

D. *The Practice of Gene Patenting Discourages Patient Participation and Thereby Limits the Fundamental Resource for Genetic Research*

Patient concern over the ultimate use of their personal tissue samples and genetic information has become a serious issue in genetic research. Patients have sued to stop use of their biological and genetic material in light of patent-holders' financial gain, undisclosed later uses, and restrictive licensing practices. *See Moore v. Regents of the Univ. of Cal.*, 793 P.2d 479 (Cal. 1990); *Greenberg*, 264 F. Supp. 2d 1064 ; *Washington Univ. v. Catalona*, 490 F.3d 667 (2007). Ignoring the role of patients in genetic research and innovation discourages patient participation, "the only irreplaceable, critical resource ... in the discovery of [a] gene." Jon Merz, *Discoveries: Are There Limits on What May Be Patented?*, Who Owns Life? (2002).

The Canadian College of Medical Geneticists' official statement on gene patents addresses the needs of patients and other research participants who donate their time and personal biological samples "altruistically with a motivation to promote better care for others." Julie Richer et al., *CCMG statement on gene patents*, 82 Clin. Genet. 405-407 (2012). Granting a patent to a single individual or entity in effect "fails to recognize the essential public investment in this process of collaboration and discovery . . . [and] fails to respect the wishes of patients who generously contribute with the hope of helping others," an oversight that "may have damaging effects on the future of genetic medicine by limiting the willingness of our patients to participate in future research endeavors." *Id.*

Indeed, as the role of personalized medicine and whole-genome sequencing rapidly expands, some geneticists support transparency between researchers and patients as not only a moral and ethical imperative but also in the best interest of researchers and innovation. Misha Angrist, *You never call, you never write: why return of 'omic' results to research participants is both a good idea and a moral imperative*, 8(6) PMC 651-657 (Dec. 2011).

II. UNDER THIS COURT'S JURISPRUDENCE, ISOLATED GENE SEQUENCES ARE NOT PATENTABLE SUBJECT MATTER

Despite the broad language set forth in 35 U.S.C. § 101, the scope of what is eligible for patent protection is not limitless. This Court consistently recognizes boundaries of eligibility for patent protection by identifying general areas and subjects that are off limits to private monopolization. These subjects for exclusion are often described in terms including "natural phenomena," "laws of nature" and "abstract ideas." *See Diamond v. Diehr*, 450 U.S. 175 (1981); *Parker v. Flook*, 437 U.S. 584 (1978). But the Court has used other phrases such as "products of nature,"[4] "physical phenomena"[5] and "forces of nature"[6] interchangeably with "natural phenomena" and "laws of nature."

The rationale behind such exceptions is rooted in the idea that innovation requires unfettered access to a strata of basic concepts and natural phenomena that are prerequisite to and foundational of any advances in science and commerce. In *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948), the Court explained that "patents cannot issue for the discovery of the phenomena of nature ... The qualities of [nature] ... are part of the storehouse of knowledge of all men. They are manifestations of laws of nature, free to all men and reserved exclusively to none." *Id.* at 130.

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[4] *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 130 (2001); *Diamond v. Chakrabarty*, 447 U.S. 303, 311 (1980).

[5] *Bilski v. Kappos*, 130 S. Ct. 3218, 3221 (2010); *Chakrabarty*, 447 U.S. at 309.

[6] *Dolbear v. Am. Bell Tel. Co.*, 126 U.S. 1, 532 (1888).

In *Mayo*, this Court reaffirmed that patent eligible subject matter under § 101 is limited by exclusions for natural phenomena, laws of nature, and abstract ideas, and reiterated the rationale for these exclusions:

> "Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." And monopolization of those tools through the grant of a patent might tend to impede innovation more than it would tend to promote it.

Mayo, 132 S. Ct. at 1293 (quoting *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)).

With these fundamental concerns in mind, this Court held *Mayo's* patent claims invalid because they effectively did nothing more than describe natural phenomena, *i.e.* correlations governed by natural laws. Steps such as administering an amount of the drug, determining the metabolite concentration, and inferring the need for a change in dosage contributed nothing inventive to the correlations governed by nature that lay at the core of the claimed invention. "[A] process that focuses upon the use of a natural law [must] also contain other elements or a combination of elements, sometimes referred to as an 'inventive concept,' sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself." *Id.* at 1294 (citing *Flook*, 437 U.S. at 594). Focusing on the absence of an "inventive concept," this Court concluded that well-known procedures for administering and determining contributed nothing of ingenuity to the claims.

A. *The Federal Circuit's Misapplication of This Court's Precedents*

The Federal Circuit majority has now twice concluded that Myriad's isolated DNA claims were patentable subject matter by virtue of being "isolated" from their natural environment of the human genome. *Association for Molecular Pathology v. USPTO*, 689 F.3d 1303 (Fed. Cir. 2012). According to the majority's opinion, isolation requires the breaking of covalent bonds at each end of a gene segment and thereby results in a composition having "markedly different characteristics" from the characteristics of the same sequence of nucleotides occurring in the larger genome. *Id.* at 1328. Although the Federal Circuit relied on the language of *Chakrabarty*, it deviated significantly from the analytic approach taken by *Chakrabarty* and its predecessor, *Funk*

Bros., both of which relied heavily on a consideration of the functional properties of organic compositions.

In *Funk Bros.*, this Court acknowledged that the claimed composition of bacteria was new and useful, but concluded that "[i]t is no more than the discovery of some handiwork of nature and hence is not patentable." *Id.* at 131. Significantly, the Court did not address the structural characteristics of the composition in determining whether it was a product of nature as opposed to a human manufacture. Instead, the Court observed:

> The bacteria *perform* in their natural way. Their use in combination does not improve in any way their natural functioning. They serve the ends nature originally provided and act quite independently of any effort of the patentee.

Id. (emphasis added). Under a similar analysis, this Court in *Chakrabarty* held that patent claims for a genetically-enhanced bacterium capable of decomposing oil more effectively was a human manufacture and therefore fell within subject matter patentable under § 101. In reaching this decision, the Court said nothing about chemical or structural differences in explaining how the claimed bacteria were markedly changed. Instead, it differentiated the claimed subject matter by observing that it had a petroleum degrading capability "which is possessed by no naturally occurring bacteria." *Chakrabarty*, 447 U.S. at 305.

The analysis in both *Funk Bros.* and *Chakrabarty* turned on an assessment of whether the claimed invention described any performance advantages beyond those inherent in the natural components. The claimed invention in *Funk Bros.* was not patentable because it described nothing more than a new means of packaging natural components whose natural tendencies remained unaltered. In contrast, the new bacterium in *Chakrabarty* fell on the side of human manufacture because its utility and suitability for claimed purposes derived from a property that did not occur in any bacteria naturally.

Judged against this analytic framework Myriad's composition claims are more similar to those considered in *Funk Bros.* Isolated human gene sequences, regardless of the packaging, whether extracted from cells or extracted and further purified into cDNA, are structurally and functionally identical to human gene sequences as they naturally occur. The characteristics and function of a gene reside in the gene sequence—that is, the A's, C's, G's, and T's that code for the expression of a specific protein. These characteristics and functions (the active portion of the gene sequence) have not been changed in "isolated" DNA. The person claiming ownership of an isolated gene is seeking a monopoly on its natural functions—the ability of a gene sequence to anneal to its complementary strand (which allows diagnosis) and the ability to produce proteins. Just as the utility of the claimed invention in *Funk Bros.* was reducible to the natural behavior in each of the components, the claimed utility of isolated gene sequences resides in the natural order and behavioral properties of the nucleotide sequences and depends upon those properties remaining substantially unchanged.

The Federal Circuit majority essentially reduces the "markedly different characteristics" analysis of *Chakrabarty* to a test of whether *any* human intervention has left *any* chemical change at the molecular level. Moreover, it appears Judge Lourie would apply this test regardless of the description used in the claims of the asserted invention and regardless of what field of art or science is at issue. In fact, with a simple statement Judge Lourie dismissed the relevance of the field of genetics and functional properties of the "isolated DNA":

> We recognize that biologists may think of molecules in terms of their uses, but genes are in fact materials having a chemical nature and, as such, are best described in patents by their structures rather than by their functions.

Ass'n for Molecular Pathology, 689 F.3d at 1330. There is nothing in *Chakrabarty* or *Funk Bros.* to support or even to suggest Judge Lourie's approach to the interpretation of composition claims or to support his selection of covalent bonds as the principal and defining feature of any organic compound.

Notably, the Federal Circuit majority was divided in its rationale for upholding the validity of Myriad's composition patents. Writing for the court, Judge Lourie relied on the premise that slight structural changes incidental to the process of isolation were alone sufficient to qualify the gene sequence as a product of human invention. In a concurring opinion, Judge Moore disagreed with this premise stating: "To the extent the majority rests its conclusion on the chemical differences between genomic and isolated DNA (breaking the covalent bonds), I cannot agree that this is sufficient to hold that the claims to human genes are directed to patentable subject matter." *Ass'n for Molecular Pathology*, 689 F.3d at 1341 (J. Moore concurring). Despite her reasonable rejection of Judge Lourie's premise, Judge Moore errs in her subsequent suggestion that short isolated sequences of nucleotides might be patentable by virtue of their new utility in the field of genetics.[7]

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[7] Judge Moore's concurrence in holding that isolated gene sequences are patentable subject matter appears to rest on an argument that deference is due to the USPTO's long history of allowing such patents and the settled expectations of patent holders who have relied upon such administrative guidelines. As Judge Bryson's dissent aptly points out, the USPTO does

Although Judge Moore's appeal to new utility is not misplaced, her argument fails to connect the new utility of an isolated gene segment with any contribution of human ingenuity. The only human intervention at issue in this case is the *process* of isolation. If the process of isolating genes was innovative, the process may be patent eligible, but it does nothing to transform the nucleotide sequence into something new. In the present case, however, there is nothing innovative in the isolation process and the only consequence of human intervention is a particular segment of what usually (but not always) occurs as part of a longer sequence.

Judge Moore's reasoning implausibly treats size as a defining property of isolated DNA that in turn confers patentability on an otherwise entirely natural composition. Apart from its potentially absurd consequences, this argument fails to acknowledge what the Court in *Funk Bros.* and *Chakrabarty* emphasized, namely, that classification of an organic composition as a product of human manufacture must show how its properties and utility depend upon a contribution of human ingenuity. Isolated gene sequences, no matter how short, are not patent eligible products of human manufacture because isolation does

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not have lawmaking authority and whatever expectations it may create or reliance it may have induced do not justify a continuation of practices which are contrary to legal precedent and subversive of the goals of the patent laws.

nothing to alter what is useful and beneficial about them; their utility rests primarily, if not entirely, on their natural encoding properties. Like the strains of bacteria at issue in *Funk Bros.*, the coding portions of a nucleotide sequence "serve the ends nature originally provided and act quite independently of any effort of the patentee" regardless of how they are formatted. *Funk Bros.*, 333 U.S. at 131.

B. *Application of* Mayo Collaborative Servs. v. Prometheus Labs., Inc., *to the Issue of Genetic Sequence Patents*

If *Funk Bros.* and *Chakrabarty* guide away from a narrow concern with structural chemical differences in assessing patent eligibility of biological technology, this Court's decision in *Mayo* addresses the question of how much change or difference is "marked" and sufficient to qualify as a transformation from nature to human contrivance.

In *Mayo*, this Court posed the question of whether: "the patent claims add *enough* to their statements of the correlations to allow the processes they describe to qualify as patent-eligible processes that *apply* natural laws?" *Mayo*, 132 S. Ct. at 1297. The correlative question in this case is whether the process of isolating DNA and the attendant changes that occur as a consequence of isolation make it different *enough* to *transform* it in any defining way. Based on this Court's reasoning in *Funk Bros.*, *Chakrabarty*, and now *Mayo*, the answer is clearly no.

Myriad's claims are directed to the natural genomic sequence which has been isolated through a routine process into a conventional format or package. In *Mayo*, this Court clarified that it is not *enough* to base patent eligibility on elements that "add nothing specific to the laws of nature other than what is well-understood, routine, conventional activity, previously engaged in by those in the field." *Mayo*, 132 S. Ct. at 1299.

Isolating a natural substance is not an inventive step but rather a routine and conventional process. As the Federal Circuit recognized in *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293 (Fed. Cir. 2007), "isolation of interesting compounds is a mainstay of the chemist's art," and that "[i]f it is known how to perform such an isolation doing so 'is likely the product not of innovation but of ordinary skill and common sense.'" *Id.* at 1302 (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)).

Even if the process or method of isolation itself were not routine but somehow inventive, this would not imply a transformation in the claimed subject matter of a nucleotide sequence. As the Court in *Funk Bros.* made clear, the act of repackaging organic compositions without changing their natural tendencies and functional properties is not sufficient to establish a patent claim for the natural components themselves. In the present case, the structural changes that occur as a consequence of isolation—breaking covalent bonds—have no bearing on what DNA is or does. Such changes do not alter defining *properties* of DNA as described in the patent or as interpreted by a person of skill in the art of genetics.

Specifically, the patents at issue do not teach the importance or value of the terminal points of the isolated DNA. The irrelevance of these granular changes to the claimed invention is further underscored by the fact that some claims cover numerous compositions which differ one from another in the molecular structure of their terminal points. For example, claim 6 of the Patent No. 5,747,282 for "an isolated DNA having at least 15 nucleotides of the [nucleotide sequence set forth in SEQ ID NO:1]" covers over 17 million compositions at least 15 nucleotides long within the 5,914 nucleotide sequence of SEQ ID NO:1. The 17 million compositions are claimed irrespective of variation in the molecular structure of their terminal ends. Such differences are irrelevant to the patent claims and the properties of the nucleotide sequence or coding function that defines DNA. Moreover, such differences are irrelevant to the purported utility of the claimed subject matter.

In sum, *Mayo* teaches that identifying de minimis molecular differences in the ends of a complex polymer chain is not *enough* to merit patent protection if such differences bear no relationship to any change in the properties claimed or any inventive concept or solution to a problem. *Mayo* read in conjunction with *Funk Bros.* and *Chakrabarty* compels the conclusion that merely isolating a natural sequence of nucleotides from the human genome by a routine process into a scientifically conventional format does not sufficiently alter the natural properties of DNA to qualify "isolated DNA" as patentable subject matter.

C. *The Intellectual Labor Required to Discover and Isolate a Genetic Sequence Does Not Justify Patent Protection for the Genetic Sequence*

Myriad has placed great emphasis on its research on genetics and the complexities of identifying useful genetic sequences. However, these are irrelevant to a determination of whether genetic sequences are patent eligible subject matter. Regardless of the intellectual labor required for discovery of natural laws and useful products of nature, such discoveries must remain accessible to assure their use in future science and innovation. Justice Breyer's statements in dissent in *Laboratory Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124 (2006) further elaborate on the reasons for recognizing the exceptions to patentable subject matter regardless of the effort, cost or value of the discovery:

> The justification for the principle does not lie in any claim that "laws of

> nature" are obvious, or that their discovery is easy, or that they are not useful. To the contrary, research into such matters may be costly and time-consuming; monetary incentives may matter; and the fruits of those incentives and that research may prove of great benefit to the human race. Rather, the reason for the exclusion is that sometimes too much patent protection can impede rather than "promote the Progress of Science and useful Arts," the constitutional objective of patent and copyright protection.

Id. at 136 (Breyer, J., dissenting).

Regardless of the human ingenuity and labor required to isolate, extract or purify a segment of human DNA, the sequence of nucleotides remain a product of nature. As stated by this Court over a century ago:

> There are many things well known and valuable in medicine or in the arts which may be extracted from ... substances. But the extract is the same, no matter from what it has been taken. A process to obtain it from a subject from which it has never been taken may be the creature of invention, but the thing itself when

> obtained cannot be called a new manufacture.

American Wood-Paper Co. v. Fibre Disintegrating Co., 90 U.S. (23 Wall.) 566, 593-94 (1874).[8]

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[8] *See also Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293 (1884) (finding artificial alizarine derived from a precursor substance and having the same properties as those found in natural alizarine was not patentable); *Ex parte Latimer*, 1889 Dec. Comm'r Pat. 123 (finding purified pine needle fiber not patentable).

AMICUS
CURIAE
BRIEF

Supreme Court, U.S.
FILED
MAR 14 2013
OFFICE OF THE CLERK

No. 12-398

In the Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,

Petitioners,

v.

MYRIAD GENETICS, INC., ET AL.,

Respondents.

On Writ of Certiorari to the
United States Court of Appeals for the Federal Circuit

BRIEF OF *AMICUS CURIAE* DR. ANANDA MOHAN CHAKRABARTY IN SUPPORT OF RESPONDENTS

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INTEREST OF *AMICUS CURIAE*[*]

Dr. Ananda Mohan Chakrabarty is the inventor of the human-made bacteria, useful for treating oil spills, that this Court found was patent-eligible in *Diamond v. Chakrabarty*, 447 U.S. 303 (1980). Following that case, Dr. Chakrabarty has remained interested in patent law and has written several articles discussing 35 U.S.C. § 101 and its application to patenting human genes. *See, e.g.*, Arsenio M. Fialho & Ananda M. Chakrabarty, *Patent controversies and court cases: cancer diagnosis, therapy and prevention*, 13 CANCER BIOL. THER. 1229 (2012).

Dr. Chakrabarty is a Distinguished University Professor at the University of Illinois at Chicago in its Department of Microbiology and Immunology. He is an inventor on 25 U.S. patents and has founded two companies applying his research to developing anti-cancer therapies. He has also advised the United States, the United Nations, NATO, and other foreign governments on scientific and legal matters.

Dr. Chakrabarty's current research is focused on using bacterial proteins to treat and prevent cancer. His research has shown that a protein called azurin has great promise for treating breast cancer and other diseases. The disclosures in the Myriad patents, and others like them, can be used to identify people who may benefit from clinical testing of azurin.

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[*] No counsel for a party authored this brief in whole or in part, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amicus* or his counsel made a monetary contribution to its preparation or submission. Petitioners filed a letter with the court consenting to the filing of any *amicus* brief. Respondents have consented to the filing of this brief.

INTRODUCTION

Cancer is a scourge that we must fight. Nearly all cancers are due to mutations in the human genome. Isolated human genes reflecting those mutations are among the best tools for diagnosing the risk a patient will develop cancer, and for designing drugs to treat the cancer or prevent its emergence. The mutations are challenging and expensive to identify and to characterize. But, once isolated, they possess a specific, credible, and substantial utility absent in nature. Myriad's patents to the isolated *BRCA1* and *BRCA2* mutations, for example, enable doctors to identify women at a high risk of breast or ovarian cancer, allowing early detection and intervention. The isolated mutations enable researchers to develop drugs targeted to fighting the cancer. And the isolated mutations enable scientists, including myself, to identify women who might benefit from new therapies that can arrest or prevent cancer.

"Are human genes patentable?" I submit the answer should be yes for isolated portions of genes that possess a specific, substantial, and credible utility different from what is found in nature. The uses of the isolated *BRCA1* and *BRCA2* mutations meet this requirement. Relying on utility as the dividing point is consistent with this Court's precedent, the text of § 101, and the PTO Guidelines. It also ensures that patents encourage the development of useful technology but do not tie up "wild-type" genes or isolated genes that have not been applied to a useful end.

The Court should not require an isolated gene (*i.e.*, a gene detached and separated from the adjoining genes in the chromosome) to have any particular degree of structural difference from what exists in nature to be patentable, aside from the differences identified by the Federal Circuit. Seemingly small structural changes to biological substances often cause major changes to function. Focusing on a substance's function, rather than its structure, will ensure that patents promote the disclosure and production of useful inventions.

Any concerns that patents on isolated human genes with a specific utility will impede research and medical treatment can be addressed by appropriately tailoring the remedies for patent infringement. Current law provides at least two ways to do this.

First, after *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388 (2006), district courts often cite the public interest to deny injunctions in patent cases and allow the defendant to continue its activities in exchange for a royalty set by the court. So injunctions will almost always be unavailable against researchers who seek to advance scientific knowledge. And they may even be unavailable against competitors if the facts show it would be better for patients, such as by improving access to accurate test results.

Second, the Bayh-Dole Act, which sets rules for patenting the fruits of federally-funded research, gives the funding agency the right to "march-in" and grant compulsory licenses to ensure effective use of the technology or to benefit public health and safety. A significant percentage of patents to isolated genes are covered by this provision.

These case-by-case mechanisms for choosing between exclusion and a compulsory license are superior to an inflexible rule that precludes all patents on all isolated, useful genes. They ensure patent rights are tailored to the public interest without jeopardizing private investment in life-saving technology.

ARGUMENT

I. Isolated Genes With a Specific, Substantial, and Credible Utility Should Be Patentable.

A. The Legal Framework

The task of separating a patent-eligible "composition of matter" under § 101 from an unpatentable product of nature is a difficult one. All human invention, particularly in biology, starts by building upon nature's materials and laws. "Everything that happens may be deemed 'the work of nature,' and any patentable composite exemplifies in its properties 'the laws of nature.'" *Funk Brothers Seed Co. v. Kalo Co.*, 333 U.S. 127, 135 (1948) (Frankfurter, J., concurring). "Only God works from nothing. Men must work with old elements." *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 n.3 (Fed. Cir. 1985). So when has there been enough human intervention to make the resulting composition patent-eligible? I respectfully submit that threshold is crossed whenever a composition has a specific, substantial, and credible utility different from what is found in nature.

There is a long history of using utility to distinguish between the patent-eligible and ineligible. Judge Learned Hand held, over a century ago, that a patent covering isolated human adrenaline was a patent-eligible "composition of matter" based on the distinct utility of the isolated compound. *See Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95, 103 (S.D.N.Y. 1911). He explained that the patentee "was the first to make it available for any use by removing it from the other gland-tissue in which it is found and . . . it became for every practical purpose a new thing commercially and therapeutically. That was a good ground for a patent." *Id.*

This Court's cases have likewise looked to utility when assessing patent-eligibility. In *Funk Brothers*, the Court observed that "[h]e who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes. If there is to be invention from such a discovery, it must come from the application of the law to a new and useful end." *See* 333 U.S. at 130. The Court then found that a mixture that combined several naturally occurring bacteria was unpatentable in part because it produced "no enlargement of the range of their utility." *Id.* at 131.

By contrast, *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), dealt with my discovery that I could transfer multiple "plasmids" that controlled a bacterium's ability to degrade various components of crude oil into a single *Pseudomonas* bacterium that had no pre-existing capability to degrade oil. *Id.* at 305 & nn.1-2. The result was a stable and harmless bacterium with a new utility for degrading oil that had not existed before. *Id.* The Court held that my genetically-engineered bacterium was patent-eligible in part because of its "potential for significant utility." *Id.* at 310. And the Court distinguished the discussion in *Funk Brothers* that had relied on the lack of new utility to deny patent eligibility there. *Id.* Even though I had used natural materials to build my invention, the Court found it patent-eligible based on its new, significant utility.

Finally, the text of § 101 itself suggests using utility as a dividing point, stating that "[w]hoever invents or discovers any new and useful . . . composition of matter" shall be eligible for a patent. *See* 35

U.S.C. § 101. A substance that is isolated out of its natural state via a structural and functional change to the substance is "new," and, if the composition also possesses a unique utility, it is "useful" in a way that the naturally-existing thing was not. Assessing patent-eligibility without reference to whether the isolated composition possesses a unique utility would read the phrase "new and useful" out of § 101. Imposing additional requirements beyond some change from the natural structure and a specific utility would improperly read a requirement into the text of § 101 that is not there.

This Court's concerns about patents on laws of nature are squarely addressed by using utility as a touchstone of patent-eligibility. If only compositions with a new, specific utility are patent-eligible, then patent protection will be limited to applications of nature's building blocks, rather than the building blocks themselves. A "utility test" also ensures that patents are available to serve their primary function—ensuring that inventors invest in useful technologies and bring them to market—without tying up what has not yet been put to use and thereby preventing others from finding such a use.

The extent of the structural similarities and differences between what exists in nature and what is sought to be patented should not drive the analysis. Seemingly small structural changes to chemical and biological compounds often make an enormous difference in their function. Altering even a single nucleotide or amino acid in a gene or protein can make the difference between a therapeutically active molecule and a therapeutically inert one. Indeed, the genetically-engineered *bacterium* that I created and sought to patent in *Chakrabarty* had a quite similar structure to what existed in nature. It shared the same genome and internal structure as naturally occurring *Pseudomonas* bacteria and differed only by a few pieces of DNA. But those small structural differences led to a new and significant utility that made the modified bacterium patent-eligible. If Petitioners' position that a composition must have "substantial" structural differences from what exists in nature to be patent-eligible, then I would never have obtained my patent in *Chakrabarty*.

B. The Patent-Eligibility of Genes

The legal principles just discussed yield several conclusions about the patent-eligibility of human genes. First, "wild-type" genes that exist in natural form should not be patentable because they have no special utility beyond the functions they already carry out in nature. Moreover, patent protection should not be extended to isolated genes that do not possess a specific, credible utility. Patents to such compositions would cover nothing but nature's building blocks because they would not impart any particular usefulness that was created by human intervention and manipulation. New, isolated genes that have a specific, substantial, and credible utility, however, should be patent-eligible.

The U.S. Patent & Trademark Office, when analyzing the patent-eligibility of human genes, reached these same conclusions. After an extensive notice and comment period, the agency issued guidelines in 2001 for examiners to apply when assessing patentability under § 101's "utility" requirement. *See* 66 Fed. Reg. 1092 (Jan. 5, 2001). Some of the public comments urged the agency "not to issue patents for genes on the ground that genes are not inventions," *id.* at 1092, the same argument Petitioners make here. The agency rejected this argument and adopted the position I am advocating here, providing the following explanation:

> If a patent application discloses only nucleic acid molecular structure for a newly discovered gene, and no utility for the claimed isolated gene, the claimed invention is not patentable. But when the inventor also discloses how to use the purified gene isolated from its natural state, the application satisfies the "utility" requirement. That is, where the application discloses a specific, substantial, and credible utility for the claimed isolated and purified gene, the isolated and purified gene composition may be patentable.

Id. at 1093. The agency cited, among other things, Judge Hand's decision in *Parke-Davis* as support for its conclusion. The Guidelines, which are the work of an agency with specialized expertise in this area, have been consistently applied for over a decade. They have strong persuasive force here.

Applying these principles, the Myriad patent claims that cover isolated DNA with the *BRCA1* and *BRCA2* mutations associated with an increased risk of breast or ovarian cancer should be patent-eligible because they have a specific, substantial, and credible utility. Locating and characterizing both the genes and the genetic mutations involves significant human effort. Once the mutations are isolated, they can be used to determine whether a woman is predisposed to these types of cancer, and to screen potential drug candidates to fight the cancer as it emerges or to prevent it from ever starting. These uses for the isolated genes with the relevant mutations would not exist without the inventors' efforts.

And they are different than what DNA is used for in nature, which is to store information and direct protein synthesis.

Indeed, a collection of federal agencies applying the Affordable Care Act recently confirmed the utility of Myriad's testing. The Act requires that all non-grandfathered private insurance plans cover, without imposing any cost-sharing, a list of preventive services to be determined by the U.S. Preventive Service Task Force. *See* 42 U.S.C. § 300gg-13. Both Myriad's genetic counseling and its actual testing for the mutation are now included as a preventive service covered by this provision. *See, e.g.*, *BRCA Testing Granted Preventive Care Designation Under the Affordable Care Act,* http://tinyurl.com/b9y5boa (last visited Mar. 14, 2013). As a result, "women who are members of non-grandfathered insurance plans, who are determined to be high risk by their healthcare providers, will have no out-of-pocket costs including copays, deductibles, and coinsurance when ordering" Myriad's testing. *Id.* Not only does this show that Myriad's testing will be widely available, it demonstrates that the relevant agencies with expertise have recognized the usefulness of Myriad's testing. And that testing is made possible only by Myriad's isolation of the BRCA mutations. This is the same sort of real-world application this Court has held confers patent-eligibility. *See Diamond v. Diehr*, 450 U.S. 175 (1981) (holding the application of the Arrhenius equation to a process of curing rubber is patent-eligible under § 101).

There is more. Myriad's patented *BRCA1* and *BRCA2* mutations have another exciting new, specific use: identifying women who could benefit from new anti-cancer therapies. A young woman who tests positive for the mutation currently faces a devastating choice—should she live in fear knowing that she will probably develop cancer, or should she immediately have her breasts and reproductive organs surgically removed to eliminate the risk of cancer? I, along with others in the field, am working toward a better option.

We have recently demonstrated that a bacterial protein (azurin), and a peptide derived from it (p28), were able to selectively enter and kill human cancer cells while not attacking healthy cells. Although azurin has not yet been clinically tested, p28 showed significant beneficial effects in Phase I clinical trials involving 15 patients with Stage IV cancer, which is the most advanced state. *See, e.g.*, Fialho & Chakrabarty, 13 CANCER BIO. & THER. at 1231, and references cited there. Not only is p28 free from any toxicity, but, in two patients, it showed significant beneficial effects, including complete regression of tumors that were resistant to all conventional drugs. *Id.* In separate laboratory experiments, we have demonstrated, and in fact patented, the additional role of p28 in preventing the onset of pre-cancerous lesions in mouse mammary cells. *See, e.g.*, U.S. Patent No. 8,232,244. We have thus clearly demonstrated that a potential candidate drug such as p28 not only does not demonstrate any significant toxicity, unlike most chemotherapeutic drugs, but also has both cancer therapeutic and cancer preventive activity. *Id.*

The screening for *BRCA1* and *BRCA2* mutations can be used to identify women who would be excellent candidates for additional research into the anti-cancer and cancer-preventive potential of p28. If women with the mutations who are taking p28 experience lower rates of cancer than are usually associated with the mutation, this would be strong evidence that p28 could be a successful treatment for ovarian and breast cancer, or could stop those cancers before they emerge. *Id.* Myriad's isolation of the *BRCA1* and *BRCA2* mutations can thus be applied to achieve a major breakthrough in treating breast and ovarian cancer patients for a possible permanent cure.

The unique utility of *BRCA1* and *BRCA2* mutations makes them different from the examples relied upon by Petitioners and Judge Bryson's dissenting opinion below to argue against patentability. A human kidney that has been removed (isolated) from the body does not have any utility apart from that which existed in nature. Neither does a polished diamond, nor gold taken from a stream, nor a leaf snapped from a tree. But the Myriad patents covering the isolated *BRCA1* and *BRCA2* mutations allow for genetic testing and drug screening for a permanent cure for cancer that would be impossible with non-isolated mutation-harboring DNA as it exists in the genome of a vulnerable woman. For that reason, they should be patent-eligible.

C. The Practical Consequences

There are significant real-world benefits to recognizing as patent-eligible any isolated gene with a specific, substantial, and credible utility. Consider what might have happened if patent protection for the *BRCA1* and *BRCA2* mutations were unavailable. Industry funding would have disappeared because there would be no guarantee that any investment into characterizing the mutation could be recouped. In the absence of patent protection, others could wait for an initial investor to characterize the mutations, and then they could copy the technology and sell it to the public at a lower price that the original investor—who would be burdened with the large up-front R&D costs—couldn't match. As a result, there would never be an initial investor. Although there would still be government funding for such research, it would not cover the shortfall. Moreover, government funding would be directed mostly to universities, where fundamental basic research is conducted more for publications than for problem solving, and not to entities capable of commercializing the technology.

The possible results of this funding shortfall? Researchers may never have located the mutations. Myriad may never have been able to bring tests for the mutations to market. And researchers like myself may never have been able to use the mutations to identify patients who would benefit from new anticancer and cancer-preventive therapies.

Patent protection for isolated genes with a specific, credible utility not only drives technology to market, but it also encourages "the public disclosure of new and useful advances in technology," an important goal of patent law. *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 63, (1998). Those who isolate useful genetic mutations can currently disclose their findings to the public in a patent application while obtaining a limited window of protection that will enable them to recover their investments. Without the option of patent protection, companies that make major investments in insolating genetic mutations will have every incentive to keep their work a trade secret. *See, e.g.*, William M. Landes & Richard A. Posner, THE ECONOMIC STRUCTURE OF INTELLECTUAL PROPERTY LAW 328-32 (2003). Such secrecy would divert resources away from the fight against cancer, as companies would spend money protecting their information rather than re-investing in further research. *Id.* It would also lead to duplicated efforts, as multiple companies might repeat the same work, unable to build on one another's efforts or to diversify their efforts and each pursue different mutations. And it would impede others from using that research as a jumping off point to design new drugs that may be able to eradicate cancer altogether—as in the case of the p28 research discussed above.

Myriad's patents are not alone in having enabled a company to bring technology to market. DNA-related patents have led to many new medical treatments that would not have existed without patent protection. One early success was Genentech's use of recombinant DNA—*i.e.*, human-made DNA synthesized by piecing together natural material from multiple sources—to direct microorganisms to produce insulin. *See, e.g.*, U.S. Patent No. 4,704,362, and others in the portfolio. Genentech licensed the patents to Eli Lilly, which used the technology to market the first form of synthetic human insulin, a drug called Humulin. Lilly began selling the product in 1982, and it quickly proved to be superior to the existing animal insulin products, all of which were more likely to produce an allergic reaction. *See, e.g.*, Irving S. Johnson, *Human insulin from recombinant DNA technology*, 219 SCIENCE 632 (1983) (describing the history). By 2006, human insulin or insulin analogs had replaced animal insulin products in the United States. *See, e.g.*, *Insulin*, http://www.diabetesdaily.com/wiki/Insulin (last visited Mar. 14, 2013.). These achievements would not be possible without patent protection, which ensured that Genentech and Lilly recouped their significant investments in bringing this technology to market.

Whatever the Court does in this case, it should avoid broad pronouncements that render entire categories of patents invalid. If the Court were to simply answer the question "are human genes patentable" with a categorical "no," it would, to be sure, eliminate some bad patents. But, if the Court were to extend this answer to even patents involving isolated genes or recombinant DNA—which are not the same as "human genes" as they exist in nature—it would also eliminate many good patents, like Genentech's and Myriad's, which have led to medical testing and treatments that would not otherwise have been available.

There are many different types of gene patents, and the patent-eligibility of each should be analyzed on its own merits. Relying on "specific, substantial, and credible utility" as the test of patent-eligibility would give the courts the flexibility to do this. And it would ensure that good patents covering useful results are permitted while bad patents that lock up nature's building blocks before they can be put to use are prohibited.

II. The Law Already Provides Mechanisms for Compulsory Licensing of Gene Patents.

The briefs of Petitioners and some other *amici* (including Dr. James Watson) suggest broadly that permitting patents on isolated human genes with a specific utility will prevent anyone else—*e.g.*, university researchers, clinicians, and other testing laboratories—from using those genes. But, in fact, a patent does not always give its owner the right to exclude others from using the patented invention. Existing law provides multiple mechanisms by which one can obtain a compulsory license to a patent.

For one thing, this Court held in *eBay Inc. v. MercExchange, LLC*, 547 U.S. 388 (2006), that injunctions in patent cases are not automatic. Instead, a patentee seeking an injunction must prove, among other things, that "the public interest would not be disserved" by an injunction. *Id.* at 391. The lower courts, applying *eBay*, have not hesitated to deny injunctions where they disserve the public interest, including the interest in health and safety. *See, e.g.*, *Johnson & Johnson Vision Care, Inc., v. CIBA Vision Corp.*, 712 F. Supp. 2d 1285 (M.D. Fla. 2010); *Bard Peripheral Vascular, Inc. v. WL Gore & Assocs., Inc.*, 2009 WL 920300 (D. Ariz. March 31, 2009); *Advanced Cardiovascular Sys. v. Medtronic*, 579 F. Supp. 2d 554 (D. Del. 2008). So all of the concerns that Petitioners and other *amici* raise about a patient's ability to get a second opinion, the ability of other researchers to identify different mutations or alternate ways of using the claimed mutation, and the like, could be addressed in a case-specific context by the district court in deciding whether to enjoin any of that activity.

After *eBay*, the Federal Circuit had to address what should happen in cases where an injunction does not issue. That court held that, when an injunction is denied, the district court may allow the defendant to continue to use the patented technology if it pays an ongoing royalty to the patent holder. *See Paice LLC v. Toyota Motor Corp.*, 504 F.3d 1293, 1313-16 (Fed. Cir. 2007). This is, in effect, a compulsory license. Although the standards for determining the appropriate royalty rate are in flux, district courts now routinely impose compulsory licenses in cases where an injunction is denied. *See, e.g.*, *Boston Scientific Corp. v. Johnson & Johnson*, 2009 WL 975424 (N.D. Cal. Apr. 9, 2009); *Orion IP, LLC v.*

Mercedes-Benz USA, LLC, No. 05-cv-322, Doc. 638 (E.D. Tex. Mar. 28, 2008). So if the district court found that an injunction was not in the public interest based on one of the concerns articulated by Petitioners and other *amici*, it could impose a compulsory license at a rate appropriate to compensate the patentee, but low enough to ensure that "infringing" activity deemed to be in the public interest could continue. For some types of non-commercial activity that pose little harm to the patentee, like academic research, the royalty rate would likely be close or equal to zero.

For another thing, when patents result from federally-funded research, the funding agency can "march-in" and grant a compulsory license to the patent in several situations. *See* 35 U.S.C. § 203(a). Those situations include cases in which "action is necessary to alleviate health or safety needs which are not reasonably satisfied by" the patentee, *id.* at § 203(a)(2), or where the patentee "has not taken, or is not expected to take within a reasonable time, effective steps to achieve practical application of the subject invention in such field of use." *Id.* at § 203(a)(1). The funding agency presumably possesses specialized expertise about the technology covered by the patent and whether a license is necessary to protect the public interest.

These march-in rights are particularly significant for patents to isolated human genes. Many DNA patents are owned by universities that obtained them through federally-funded research. One article reports that non-profit institutions owned between one-third and one-half of all DNA patents that issued from 1980-2003. *See* Robert Cook-Deegan & Christopher Heaney, *Patents in Genomics and Human*

Genetics, 22 ANN. REV. GENOMICS HUM. GENETICS 383 (2010). Another study, relying on data through 2005, found that 13 of the 30 entities holding the most DNA patents were non-profit universities. *See* Lori Pressman, et al., *The Licensing of DNA Patents by Large U.S. Academic Institutions: An Empirical Survey*, 24 NATURE BIOTECHNOLOGY [illegible]1, 33 (2006). The study also found that the government had an interest in 50% of DNA patents owned by the top 30 academic institutions, and had an interest in 13.7% of all DNA patents. *Id.* at 36. And, indeed, the patents at issue in this case are owned by the University of Utah and resulted from research that was sponsored in part by the National Institutes of Health. *See* 702 F. Supp. 2d 181, 202 (S.D.N.Y. 2010).

These mechanisms show that making isolated human genes eligible for patent protection will not exclude others from using them for all purposes. Instead, a district court or the funding agency (or both) has discretion to assess, on a case-by-case basis, whether exclusion is the appropriate remedy, or whether damages alone will suffice. Flexibility will lead to more informed decision-making, as the court or agency will be able to consider the evidence on the specific patent before it and determine the appropriate remedy for any infringement.

This Court has endorsed such flexibility in patent law, eschewing categorical rules in a variety of contexts, including § 101. *See, e.g., Bilski v. Kappos*, 131 S.Ct. 3218 (2010) (declining to hold that business method patents are categorically ineligible for patent protection); *KSR v. Teleflex Co.*, 550 U.S. 398 (2006) (rejecting the rigid teaching, suggestion, or motivation test for obviousness); *eBay*, 547 U.S. at 391-94 (holding there is no presumption that an injunction should issue). A similar approach is appropriate here. By contrast, a sweeping pronouncement that no isolated genes are eligible for patent protection would upset existing expectations, discourage future investment, and could slow or prevent countless new inventions in this promising area of technology. This Court's usual case-by-case approach to crafting rules of patent law is the far better one here.

CONCLUSION

For the reasons above, *amicus* encourages the Court to hold that isolated human genes with a specific, substantial, and credible utility, such as those covered by the Myriad patents, are patent-eligible under § 101.

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AMICUS
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BRIEF

Supreme Court, U.S.
FILED
JAN 31 2013
OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY,
ET AL.,

Petitioners,

v.

MYRIAD GENETICS, INC., ET AL.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF FOR CLS BANK INTERNATIONAL AS AMICUS CURIAE IN SUPPORT OF NEITHER PARTY

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INTEREST OF AMICUS CURIAE[*]

Chartered under the Federal Reserve Act, CLS Bank International ("CLS") was established in the late 1990s by the international banking community, in cooperation with a number of central banks, to mitigate settlement risk in the foreign exchange market—the risk that one counterparty to a transaction will transfer its funds and the other will fail to do so—by ensuring that both parties have fulfilled their respective obligations before directing the exchange of currencies. CLS was accused of infringing four patents that, a district court ruled, claim only "abstract ideas" related to computer-implemented risk mitigation and thus are patent-ineligible under 35 U.S.C. § 101 as construed in *Bilski* v. *Kappos*, 130 S. Ct. 3218 (2010). *CLS Bank Int'l* v. *Alice Corp. Pty. Ltd.*, 768 F. Supp. 2d 221, 243-48 (D.D.C. 2011). The Federal Circuit is reviewing that decision *en banc*. *See CLS Bank Int'l* v. *Alice Corp. Pty. Ltd.*, 484 F. App'x 559 (Fed. Cir. 2012).

While this Court's precedents have never suggested that the Section 101 inquiry is technology-dependent, some *amici* in the Federal Circuit appeal have argued that this Court's patent-eligibility decisions in fields other than computer science—and, in particular, *Mayo Collaborative Services* v. *Prometheus Labs, Inc.*, 132 S. Ct. 1289 (2012)—do not apply equally to computer-implemented methods. This case presents the Court with the opportunity to reaffirm that Section 101 mandates the same threshold inquiry regardless of whether a claim is drawn to a law of nature, natural phenomenon, or abstract idea.

---

[*] Pursuant to Rule 37.6, *amicus* states that no counsel for any party authored this brief in whole or in part, and that no person or entity other than CLS or its counsel made a monetary contribution to the preparation or submission of this brief. The parties have consented to the filing of this brief and copies of their letters of consent have been lodged with the Clerk of the Court.

SUMMARY OF THE ARGUMENT

The Court has treated laws of nature, natural phenomena, and abstract ideas as equivalently ineligible for patenting because they encompass the fundamental building blocks upon which scientific and industrial endeavors are based and thus must remain free for anyone to use. Indeed, there is no principled basis for distinguishing among them for purposes of determining patent-eligibility. The predictability and certainty of our unitary patent system would best be served by continuing to apply Section 101 the same to all patent claims.

ARGUMENT

This Court "has long held" that "'[l]aws of nature, natural phenomena, and abstract ideas' are not patentable." *Mayo Collaborative Services* v. *Prometheus Labs, Inc.*, 132 S. Ct. 1289, 1293 (2012) (quoting *Diamond* v. *Diehr*, 450 U.S. 175, 185 (1981)). These are the building blocks of "Science and Useful Arts." *See Diamond* v. *Chakrabarty*, 447 U.S. 303, 307 (1980) (quoting U.S. Const. art. I, § 8, cl. 8). "A principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented, as no one can claim in either of them an exclusive right." *Diehr*, 450 U.S. at 185 (quoting *Le Roy* v. *Tatham*, 55 U.S. (14 How.) 156, 175 (1853)). They must remain "free to all men and reserved exclusively to none." *Funk Bros. Seed. Co.* v. *Kalo Co.*, 333 U.S. 127, 130 (1948). Section 101 thus obligates the

Judiciary to exercise a critical "screening function" to guard against patents that "foreclose[] more future invention than the underlying discovery could reasonably justify." *Mayo*, 132 S. Ct. at 1301, 1303.

The Court's approach to Section 101 creates "a single 'exception'" to patent-eligibility focused on a uniform "exclusionary principle." 1 Donald Chisum, Patents § 1.03[2][f] (2012) (quoting *Mayo*, 132 S. Ct. at 1293). To be sure, the Court has over time variously described the nature and number of the categories excluded from patent-eligibility. *See* Donald Chisum, *Weeds and Seeds in the Supreme Court's Business Method Patents Decision: New Directions for Regulating Patent Scope*, 15 Lewis & Clark L. Rev. 11, 28-29 (2011) (tracing the history of this Court's description of the exception to patent-eligibility). At no time, however, has the Court ever suggested that they differ substantively for purposes of analysis under Section 101.

Indeed, this Court has recognized that the labels used to describe patent-ineligibility may be interchangeable. For example, *Diehr* stated that a computer algorithm "is like a law of nature" at the same time as it noted that "[a]n idea of itself is not patentable." 450 U.S. at 185-86 (quoting *Rubber-Tip Pencil Co.* v. *Howard*, 87 U.S. (20 Wall.) 498 (1874)). Natural phenomena too bear a close relation to the other categories: bacteria and other natural products are "manifestations of laws of nature." *Funk Bros.*, 333 U.S. at 130. The recognition of this interrelationship goes back to the foundation of the patent-ineligibility doctrine. *Le Roy*, for example, involved the manmade principle of "steam power," but the Court noted that "[t]he same" rationale for excluding that principle applied to "electricity" and "any other power in nature." 55 U.S. at 175; *see also O'Reilly* v. *Morse*, 56 U.S. (15 How.) 62, 114 (1853) ("so far as patentable rights are concerned," steam power and electromagnetism "must stand on the same principles").

Accordingly, this Court has historically treated ineligibility determinations as part of a single exclusionary doctrine. For example, *Mayo*, cited *O'Reilly*, *Diehr*, *Bilski*, *Gottschalk* v. *Benson*, 409 U.S. 63 (1972), and *Parker* v. *Flook*, 437 U.S. 584 (1978), for the proposition that a claim must contain an inventive concept, not mere post-solution activity or limitations to a technological environment. 132 S. Ct. at 1294. *Diehr* borrowed language from *Funk Bros.* and explicitly held that "the same principle" that governs claims to products of nature also applies to processes. 450 U.S. at 188 n.11. *Flook* held that "*Mackay Radio* and *Funk Bros.* point to the proper analysis in this case." 437 U.S. at 591. And *Benson* drew its analysis from cases involving multiple technological environments. 409 U.S. at 67-71.

There is no principled basis under Section 101 for distinguishing between abstract ideas, laws of nature, and natural phenomena. They all share an underlying "functional concern" that "is a *relative* one: how much future innovation is foreclosed relative to the contribution of the inventor." *Mayo*, 132 S. Ct. at 1303 (emphasis in original). Reflecting this concern, the Court has uniformly held that ineligible claims remain ineligible regardless of the addition of field of use limitations, limitations to a particular technological environment, or a "narrow and specific" application. *Id.* at 1297, 1301, 1303. Such limitations do not give the public "creative value" sufficient to justify the "future innovation" such a claim threatens to impede. *Id.* at 1303. They cannot "transform the nature of the claim," regardless of whether the claim is drawn to an abstract idea, natural phenomenon, or law of nature. *Id.* at 1297.

The Court has expressly recognized that abstract ideas, laws of nature, and natural phenomena are equivalent for purposes of Section 101 analysis: "[A]ppending conventional steps, specified at a high level of generality, to laws of nature, natural phenomena, *and* abstract ideas cannot make those laws, phenomena, *and* ideas patentable." *Mayo*, 132 S. Ct. at 1300 (citation omitted; emphasis added); *see also, e.g.*, *Flook*, 437 U.S. at 593. Significantly, this Court recently vacated a decision involving a computer-implemented method in light of *Mayo*, which involved claims directed to the application of a law of nature. *Ultramercial, LLC* v. *Hulu, LLC*, 657 F.3d 1323 (Fed. Cir. 2011), *vacated sub nom. Wildtangent, Inc.* v. *Ultramercial, LLC*, 132 S. Ct. 2431 (2012).

Congress enacted a unitary patent system in which the same "general rules must govern inventive activity in many different fields of human endeavor." *Mayo*, 132 S. Ct. at 1305. Section 101 does not discriminate among different technological fields; it would make no sense to have one approach for computer-implemented methods, another for diagnostic methods, a third for isolated genetic material, and so forth. Such divergence would represent a sharp and unwarranted break from this Court's Section 101 jurisprudence, and would frustrate the certainty and predictability that inventors, examiners, and courts all require. *Cf. J.E.M. Ag Supply, Inc.* v. *Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 135 (2001) (Section 101 "is a dynamic provision designed to encompass new and unforeseen inventions").

Section 101 applies the same regardless of whether the invention implicates a natural phenomenon, law of nature, or abstract idea. This Court should continue to apply a common framework in which *all* patent claims that do not contribute enough innovation to justify their patent monopoly fail to clear the Section 101 threshold. *Mayo*, 132 S. Ct. at 1299.

CONCLUSION

Regardless of whether the judgment is affirmed or reversed, the Court should confirm that 35 U.S.C. § 101 applies uniformly across technological fields.

Respectfully submitted.

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January 31, 2013

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BRIEF

Supreme Court, U.S.
FILED
MAR 14 2013
OFFICE OF THE CLERK

No. 12-398

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to the United States Court of Appeals
for the Federal Circuit

BRIEF OF THE COALITION FOR 21ST CENTURY MEDICINE AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENTS

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QUESTION PRESENTED

Whether the isolated BRCA1 and BRCA2 DNA molecules claimed by Myriad—which do not exist in nature and are the product of human ingenuity and intervention—are patent-eligible subject matter under 35 U.S.C. § 101.

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BRIEF OF THE COALITION FOR 21ST CENTURY MEDICINE AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENTS

INTEREST OF *AMICUS CURIAE*[1]

Amicus Curiae the Coalition for 21st Century Medicine represents diagnostic technology companies, clinical laboratories, researchers, physicians, venture capitalists, and patient advocacy groups who believe that continuous diagnostic innovation is needed to enhance treatment decisions and improve patient outcomes.

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[1] Pursuant to Supreme Court Rule 37.6, counsel for *amicus curiae* states that no counsel for a party authored this brief in whole or in part, and no party or counsel for a party made a monetary contribution intended to fund the preparation or submission of this brief. Counsel's fees incurred to prepare this brief were paid by AbbVie, Inc. Otherwise, no person or entity other than *amicus curiae* or its counsel made a monetary contribution to this brief's preparation or submission. All parties consented to the filing of this brief. Copies of the letters granting consent have been filed with the Clerk.

This case concerns whether material derived from human genes—isolated DNA—is patentable subject matter under Section 101 of the Patent Act. *Amicus* believes that efforts to undermine DNA sequence patents in the United States endanger this future by pushing investors away from molecular diagnostics technology. Without their continued investment, private industry will no longer be able to support the same breadth of expensive and complex research, development, and commercialization of these critical health care products. This will cause serious harm to the well-being of patients who would otherwise benefit from personalized medicine. In view of *amicus*'s role in the genetic diagnostic field, it has a unique perspective on and a keen interest in the question presented.

SUMMARY OF ARGUMENT

I. Section 101 of the Patent Act defines patentable subject matter as "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." 35 U.S.C. § 101. However, "laws of nature, natural phenomena, and abstract ideas" are not patentable. *Diamond* v. *Diehr*, 450 U.S. 175, 185 (1981). Consequently, if the question presented in this case truly were whether "human genes" are "patentable," Pet. Br. i, the answer would be "no"; the human genome is a natural phenomenon. But Myriad's patents do not claim "human genes." They claim "isolated DNA" in a form that does not exist in nature or the human body—a lab-made, "nonnaturally occurring * * * composition of matter," a "product of human ingenuity having a distinctive name, character, and use." *Diamond* v. *Chak-*

rabarty, 447 U.S. 303, 309-310 (1980) (alterations omitted). Isolated DNA is chemically distinct from genomic or "native" DNA found in the human body; it is found nowhere in nature; and it has scientific and medical applications that native DNA does not. It is patentable subject matter even though native DNA is not.

II. Patent protection is essential to advancing human understanding of genomics and developing new genetic diagnostic and therapeutic products that will improve public health and quality of life.

A. Personalized medicine is a new field that is revolutionizing the healthcare industry by using genetic diagnostics to tailor treatments to patients' individual genetic makeups. The research and development activities needed to make discoveries in this field, to transform those discoveries into useful products, and to obtain the necessary regulatory approval for use of those products, however, is expensive, time-consuming, and risky. Given the significant investment and substantial risk required, the incentives afforded by the patent system are critical to ensuring the advancement of gene-based diagnostics and therapeutics and unlocking the potential of personalized medicine in the United States.

B. By requiring disclosure of genetic innovations—and requiring sufficient disclosure to allow others to practice the innovation—patents advance the store of human knowledge, creating springboards for further innovation. Patents allow private-sector competitors to collaborate on new advances by eliminating fears that innovative intellectual property might be appropriated. And coupling patented technologies with appropriate licensing practices has permitted the private and public sectors to collaborate and transform the fruits of academic research into products that improve public health.

III. Petitioners claim that granting protection for isolated DNA will enable patentees to prohibit all research on particular genes, and will give patentees exclusive rights over future applications that are neither disclosed in the patent nor technically achievable at the time the patent application is filed. Existing patent law doctrines, however, amply address those concerns. A statutory safe harbor allows certain research and uses that would otherwise be infringing for purposes of seeking federal regulatory approval necessary to bring competing products to market once the patent expires. And the Patent Act's written description and enablement requirements prohibit patentees from claiming exclusive rights in innovations unless they in fact developed them, disclose them, and provide a written description sufficient to permit others reasonably skilled in the art to make and use them. This Court should not distort Section 101 to address concerns that Congress has spoken to in other sections of the Patent Act.

IV. Petitioners and *amici* also argue that patents on isolated DNA inhibit innovation and restrict patient access to new diagnostics and therapeutics. The PTO, however, has been issuing patents on isolated DNA for 30 years, and the empirical evidence refutes the parade of horribles petitioners and *amici* attempt to conjure. The allegation that research is impeded is unsupported. To the extent patients have sometimes been denied access to innovative new genetic tests and treatments, that has been a result of the insurance industry's failure to keep abreast of medical advances that can help their insureds, not a limit imposed by patent protection.

ARGUMENT

I. ISOLATED DNA GENERATED THROUGH HUMAN INTERVENTION—THE COMPOSITION OF GENETIC MATTER AT ISSUE HERE—IS PATENTABLE SUBJECT MATTER

Section 101 of the Patent Act defines patentable subject matter as "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." 35 U.S.C. § 101. This Court has construed Section 101 broadly, explaining that "Congress plainly contemplated that the patent laws would be given wide scope." *Bilski* v. *Kappos*, 130 S. Ct. 3218, 3225 (2010). "[L]aws of nature, natural phenomena, and abstract ideas," however, are not patentable under Section 101. *Diamond* v. *Diehr*, 450 U.S. 175, 185 (1981). This case concerns whether a patent on a specific composition of matter derived from human genetic material—"isolated DNA"—is patentable subject matter under Section 101. Under this Court's precedent, the answer is "yes."

A. Isolated DNA Constitutes A New Composition Of Matter, Not A Natural Phenomenon

Notwithstanding petitioners' request that this Court decide whether "human genes" are "patentable," Pet. Br. i, that is not the question before the Court. If it were, the answer would be a straightforward "no." "Human genes" exist in nature, inside the human body. And it is well-settled that compositions of matter as they exist in nature—such as human genes in the form of native DNA—are not patentable subject matter. See *Diamond* v. *Chakrabarty*, 447 U.S. 303, 309-310 (1980); *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948). An inventor must actually invent something to earn the exclusive right to practice the invention. No one may patent the basic phenomena and products of nature, which are "free to all men and reserved exclusively to none." *Funk Bros.*, 333 U.S. at 130, 131.

But Myriad's patents do not claim the human genome or "native" DNA—DNA as it naturally exists inside the human body. As a result, whether "human genes" can be patented is not the proper question before the Court. Instead, the question is whether the *isolated DNA* molecules claimed by Myriad are patentable subject matter consistent with Section 101. Unlike native DNA, isolated DNA is a product of human ingenuity and intervention. Unlike native DNA, isolated DNA exists nowhere in nature. And isolated DNA, because it is distinct from native DNA, serves functions that native DNA cannot.

Native DNA in the human body consists of a molecule, comprised of multiple nucleotides, anchored within a complex and much larger genomic structure. Pet. App. 257a-263a. Multiple segments of DNA constitute a gene, the unit responsible for producing proteins encoded by the thousands of nucleotides within each gene. *Id.* at 258a-259a. Genes are arrayed on complex structures called chromosomes; forty-six chromosomes together contain the 25,000 genes in the human nuclear genome. *Id.* at 259a, 262a. The human genome, replicated within most cells in the human body in combination with the mitochondrial genome, carries all genetic material determining the hereditary traits of each person. *Id.* at 258a-259a & n.6. The linear DNA of chromosomes is held in complex 3D shapes by companion proteins to form chromatin. Proteins bound to DNA also modify expression of the genes. Those interstitial elements help determine the characteristics of native DNA; for instance, the proteins within a chromosome bind to DNA molecules and modulate their structure and function. *Id.* at 262a.

Isolated DNA molecules are different. They are not found in nature. Rather, scientists employ one of a variety of processes to isolate DNA from the cellular material in which it is embedded. Pet. App. 19a-20a; see generally Tan & Yiap, *DNA, RNA, and Protein Extraction: The Past and the Present*, J. Biomed. & Biotech., 2009. What those methods have in common is that they work radical changes on the native chromosomatic material. In nature, genes are part of a larger, undifferentiated DNA molecule. By, among other things, cleaving the covalent bonds within the sugar-phosphate backbone holding together a DNA molecule, scientists create an entirely new molecule, consisting solely of the isolated DNA, that did not exist before. Pet App. 51a. These snippets of genetic material are literally isolated from, among other things, the protein glue that influences the structure and function of native DNA. As the Federal Circuit observed, isolated DNA thus "exist[s] in a distinctive chemical form—as distinctive chemical molecules—from DNA[ ] in the human body." *Ibid.* Isolated DNA stands free not only from other elements of a native DNA molecule, but also from the larger structures of the chromosome.[2]

Isolated DNA also serves different functions than naturally occurring molecules within the human genome. Isolation of DNA has historically enabled a means of sequencing, the process of decoding the informational content of nucleotides within a gene. And as recognized in the decision below, isolated DNA also finds application as "probes" and "primers" that are used in genetic tests for the diagnosis and treatment of illness. Pet. App. 82a-84a.

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[2] Like isolated DNA, cDNA is manually divorced from the broader structures and biological functions of the human genome. cDNA differs from isolated DNA in that it is the product of further laboratory synthesis that excludes intron sequences found in native DNA. Pet. App. 20a. The creation of cDNA thus requires even more human intervention and inventiveness than isolated DNA. But that is a distinction of degree, not kind.

Indeed, for isolated DNA to function as a "probe" that detects genes associated with particular diseases or responsiveness to particular treatments, Pet. App. 264a, it must be calibrated precisely. Probes exploit the fact that a DNA strand, consisting of a sequence of nucleotide bases, will "pair" or "hybridize" predictably with a strand containing the complementary sequence (so 5'-AA-TT-3' hybridizes with 5'-TT-AA-3'). *Id.* at 265a. An isolated DNA probe can be created by exposing a DNA sequence to high heat or alkalinity, causing the familiar "double helix" structure of a DNA molecule to be disrupted, splitting the molecule into its two strands of complementary nucleotides. Alberts *et al.*, *Molecular Biology of the Cell* 8-25 (4th ed. 2002). The nucleotides of the isolated DNA probe are labeled, typically with a radioactive material or a fluorescent dye, so that they can be seen or detected later. The probe sequence is then mixed with a sample of genetic material from the patient. Any unhybridized material is removed. The laboratory then looks for the labeled nucleotides. If they remain—having hybridized with the complementary DNA sequence—that indicates that the gene being tested for was present. See Pet. App. 82a.[3] Native DNA cannot be used for probes; its nucleotide sequences are bound up with other matter and cannot hybridize with other native DNA.

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[3] An isolated DNA primer similarly latches onto a segment of native DNA, but is then typically used to replicate the target DNA billions of times over through a process called polymerase chain reaction amplification. Pet. App. 264a-265a, 271a. This allows the clinician to better analyze the sequence of the DNA in the target sample.

More important, isolated DNA probes can work only if they uniquely and closely reflect the nucleotides that comprise the gene or mutation being tested for, among the billions of undifferentiated nucleotides that comprise the human genome. If the isolated DNA probe includes excess material, that may prevent hybridization even if the genetic mutation being tested for is present; or, it may cause spurious hybridization where the mutation is not present. Likewise, if the isolated DNA probe includes too little material, false results are possible. The development and creation of isolated DNA probes that can be used to identify and treat disease thus requires the inventor to discover and then isolate the precise portion of the DNA needed to achieve a match—no more, no less. Far from reflecting an effort to clip a chunk off the double helix, isolating a particular gene is like carving out the precise shape for a key that will reliably fit in one, and only one, of a billion locks. That requires human intervention, great ingenuity, and extraordinary precision. And when someone figures out how to do that, it should be patentable.

B. This Court's Cases Confirm That Isolated DNA Developed Through Human Intervention Represents Patentable Subject Matter

This Court's decisions in *Chakrabarty* and *Funk Brothers* confirm that isolated DNA, such as the isolated BRCA genes at issue here, represent patentable subject matter.

In *Funk Brothers*, the Court addressed whether a mixed bacteria culture for inoculating legumes was patentable. 333 U.S. at 130-131. It previously had been thought that multiple strains of bacteria could not be mixed in an inoculant because they would inhibit one another; as a result, different inoculants containing different bacteria were used on different types of legumes. *Id.* at 129-130. The patentee discovered that there were certain strains of bacteria that did not have such a mutually inhibitive effect, and therefore could be mixed to create a single inoculant that could be applied to many different types of legumes. *Ibid.* This Court held that the mixed culture was not patentable. While the Court recognized that the patentee had discovered the non-inhibitive properties of the bacteria strains, the Court stressed that he did "not create [the] state of * * * non-inhibition in the bacteria." *Id.* at 130. Rather, those "qualities are the work of nature." *Ibid.* The Court noted that there was no change worked in the species of bacteria as a result of the patentee's efforts, and "no enlargement of the range of their utility"; rather, "[e]ach species has the same effect it always had," and "act[s] quite independently of any effort of the patentee." *Id.* at 131. The Court held that because the bacteria were a product of nature rather than a product of human invention, they were not patentable. *Id.* at 132.

By contrast, in *Chakrabarty*, this Court held that a human-altered bacteria was patentable subject matter under Section 101. 447 U.S. at 310. There, the inventor had inserted several plasmids into a naturally occurring bacteria that gave it the ability to break down the components of crude oil—a property "possessed by no naturally occurring bacteria." *Id.* at 305. Unlike the naturally occurring bacteria in *Funk Brothers*, the bacteria in *Chakrabarty* were "a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity having a distinctive name, character, and use." *Id.* at 309-310 (alterations omitted). The bacteria had "markedly different characteristics from any found in nature and * * * the potential for significant utility." *Id.* at 310.

Because the "discovery is not nature's handiwork," but the inventor's, it was found to be "patentable subject matter under § 101." *Ibid.*

Isolated DNA is far closer to the patent-eligible bacteria in *Chakrabarty* than the ineligible bacteria in *Funk Brothers*. Like the bacteria in *Chakrabarty*, the isolated DNA molecules coding for BRCA1 and BRCA2 exist nowhere in nature—they are "a nonnaturally occurring * * * composition of matter," *Chakrabarty*, 447 U.S. at 309, with a chemical structure distinct from any molecule found in the human body. Nor does the isolated BRCA DNA merely "serve the ends nature originally provided." *Funk Bros.*, 333 U.S. at 131. Instead, it has "markedly different characteristics" with "the potential for significant utility." *Chakrabarty*, 447 U.S. at 310. Indeed, petitioners themselves assert that isolated DNA has applications for research that genomic DNA does not. See Pet. Br. 9, 41. The isolated BRCA1 and BRCA2 genes also provide the basis for clinically useful diagnostic tools, such as probes and primers, that can detect mutations associated with a risk of breast and ovarian cancers and guide therapeutic responses. See pp. 8-9, *supra*. Those uses are related to the operation of the native BRCA1 and BRCA2 genes, but they are functionally distinct, having new medical applications that demonstrably improve survival rates and quality of life. See Schwartz *et al.*, *Long-Term Outcomes of BRCA1/BRCA2 Testing: Risk Reduction and Surveillance*, 118:2 Cancer 510, 516 (Jan. 15, 2012) ("the receipt of a positive BRCA1/2 test result is likely to have a favorable effect on long-term breast and ovarian cancer outcomes"). Unlike with the bacteria in *Funk Brothers*, the hugely beneficial applications of the isolated BRCA DNA would not exist "independently of any effort of the patentee," 333 U.S. at 131, but are made possible solely through human intervention in the creation of a new, isolated DNA molecule that did not exist before. Isolated DNA is a "product of human ingenuity," with "different characteristics" from and the "potential for significant utility" beyond genomic DNA. *Chakrabarty*, 447 U.S. at 309, 310. Accordingly, it is patentable subject matter under Section 101.

II. GENE PATENTS ARE CRUCIAL TO DEVELOPING PROMISING NEW DIAGNOSTIC TOOLS AND THERAPIES

A. Gene Patents Are Necessary To Ensure Financial Incentives To Undertake Research and Development In Emerging Fields

Personalized medicine has the promise to revolutionize the healthcare industry. It uses genetic diagnostics to determine which treatments will work for certain patients—and which will not. But it is an extremely resource-intensive and risky field. The costs of bringing a single product to market are high, and failures numerically dwarf successes. Patent protections are critical to providing the necessary financial incentives for investment in this promising field.

1. Physicians, clinicians, and researchers have long recognized that people with the same disease often respond very differently to the same treatment. Traditional medicine relies on a trial-and-error approach to that problem, prescribing different courses of treatment until finding what works best for a particular patient. Personalized medicine, by contrast, identifies in advance the treatments that most likely will work for a particular patient and those that will not. It does so by using diagnostic tests to obtain information about molecular "biomarkers"—such as gene sequence variations, gene or protein expression levels, or metabolites—that are corre-

lated with particular disease characteristics. See Personalized Medicine Coalition, *The Case for Personalized Medicine* 2-4 (3d ed. 2011), available at http://www.personalizedmedicinecoalition.org/sites/default/files/files/Case_for_PM_3rd_edition.pdf ("*The Case for Personalized Medicine*"). Tests showing that a patient possesses particular biomarkers are used for diagnosis, prognosis, predicting the future risk of disease, or selecting treatment regimens particularly suited (and excluding regimens unsuited) to that patient. *Id.* at 4-7. Patients can receive an early diagnosis, followed by highly individualized treatment that maximizes efficacy while minimizing the potential for side effects and adverse reactions that would result from undesirable treatments. *Id.* at 4-6. Health care costs decline as well, as insurers avoid paying for tests and/or treatment regimens that later prove to be unnecessary. *Id.* at 7.

As with biotechnology generally, the research and development activities needed to make advances in personalized medicine are extremely costly.[4] The first task is to find associations between a biomarker and a disease or drug response. *The Case for Personalized Medicine* 9. A company must then design a test—isolating the appropriate DNA sequence and probe—to permit identifying the relevant biomarker in a fashion that is accurate, robust, and replicable. Clinical trials are required to demonstrate and validate the clinical utility of the association. See generally Staples *et al.*, *The Role of the Academic Medical Center in Advancing Personalized Health Care* 83 ("*Advancing Personalized Health Care*"), in HHS,

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[4] In 2011, publicly traded companies in the United States invested more than $17 billion in biotechnology-related research and development. Ernst & Young, *Beyond Borders: Global Biotechnology Report 2012*, at 27 (2012).

Personalized Health Care (Nov. 2008). Bringing a single diagnostic product to market thus typically requires years of research and testing and tens of millions of dollars in investment—reaching over $100 million under certain circumstances. See *id.* at 84-85. If one adds the costs of the many, many more efforts that fail in development, fail to make it to market, or fail to succeed in the market, the costs become staggering: Only 30% of biological therapeutics that make it as far as human trials succeed, and many more never make it even that far. See, *e.g.*, Grabowski, *Follow-On Biologics*, 7 Nature Reviews Drug Discovery 479, 481 (2008). And still more therapeutics, even if technically successful, may never achieve commercial success. See, *e.g.*, Human Genetics Comm'n, *Intellectual Property and DNA Diagnostics: A Report of a Seminar on the Impact of DNA Patents on Diagnostic Innovation* 5-6 (Oct. 2010), available at http://www.institutoroche.es/web/pdf/2011/humangeneticscommision.pdf ("*Intellectual Property and DNA Diagnostics*"); *Advancing Personalized Health Care* 85.

Regulatory burdens—although often necessary—further increase costs. The FDA, for example, is increasingly requiring that diagnostic products going through the premarket approval process satisfy the same clinical and premarket criteria as those usually reserved for pharmaceuticals and medical devices. See Food and Drug Administration ("FDA"), *Draft Guidance for Industry and Food and Drug Administration Staff—In Vitro Companion Diagnostic Devices* 8-10 (July 14, 2011) ("FDA, *Draft Guidance*"); Press Release, FDA, *FDA To Host Public Meeting on Oversight of Laboratory-Developed Tests* (June 16, 2010), available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm215766.htm. Moreover, insurance companies, which pay the vast majority of health care dollars, often demand validating data before approving a test for reimbursement. See Nat'l Ctr. for Health Statistics, *Health, United States, 2011: With Special Feature on Death and Dying* 8 (2012), available at http://www.cdc.gov/nchs/data/hus/hus11.pdf. These further barriers increase costs dramatically. See *Intellectual Property and DNA Diagnostics* 5-6.

At the end of the day, the rewards for successfully running the research and regulatory gauntlets are not especially rich. Diagnostic products generally offer a very low rate of return on investment, particularly in light of the staggering amounts required for their development. See *Personalized Health Care* 83-85; see generally Kling, *Diagnosis or Drug? Will Pharmaceutical Companies or Diagnostics Manufacturers Earn More from Personalized Medicine?*, 8 EMBO Rep. 903 (2007).

2. Given those substantial costs, the high risk of failure, and the modest financial return, patents are critical to promising investors the realistic possibility of a reasonable financial return from diagnostic products. In a recent report on the subject, the President's Council of Advisors on Science and Technology concluded:

> The ability to obtain strong intellectual property protection through patents has been, and will continue to be, essential for pharmaceutical and biotechnology companies to make the large, high-risk R&D investments required to develop novel medical products, including genomics-based molecular diagnostics.

President's Council of Advisors on Science and Technology, *Priorities for Personalized Medicine* 21 (2008).

Indeed, there appears to be broad consensus among regulators, industry participants, and legal commentators that patent protections are vital "to incentivize the significant investment required" for clinical research in the area of personalized medicine. Toneguzzo, *Impact of Gene Patents on the Development of Molecular Diagnostics*, 5 Expert Op. Med. Diag. 273, 275 (2011).[5] As the Federal Circuit explained below, these are the very types of investments the patent laws are intended to promote and protect: "Patents on life-saving material and processes, involving large amounts of risky investment, would seem to be precisely the types of subject matter that should be subject to the incentives of exclusive rights." Pet. App. 44a.

Petitioners thus are mistaken to suggest that, once a clinically useful genetic test has been invented and its workings publicly disclosed, society would benefit more if the invention were left unpatented and free for all to use. See, *e.g.*, Pet. Br. 8 (asserting that, but for Myriad's patents, third parties could offer BRCA testing for free); *id.* at 45 (asserting that, but for Myriad's patents, third parties could offer BRCA testing at a lower price than Myriad). That approach begins by assuming the elephant—it starts by positing that the invention would exist even if patent protection were unavailable. In the biotechnology field, that rarely would be true. Absent the limited period of exclusivity afforded by patents, private actors could not justify the investment required to invent new genomics-based diagnostic tools. Fewer genetic tests would be available at any price.

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[5] See Nat'l Research Council, *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health* 20, 25 (Merrill & Mazza eds., 2006) ("intellectual property protection is essential to * * * enable firms to garner the sustained investments needed for diagnostic and drug development and testing"); Paci *et al.*, *Impact of DNA Patents on Pharmacogenomics Research and Development: Economic and Policy Issues*, 71 Drug Dev. Res. 485, 490 (2010) (patent protections "can stimulate private investments in an underexploited field with great potential for innovation and public health"); Sung, *Alarming Challenges Facing Medical Technology Innovation*, 6 J. Bus. & Tech. L. 35, 55-56 (2011) ("Tinkering with patent eligibility * * * may bring unforeseeable consequences, including the unfortunate chilling of future innovation.").

B. Patents Promote Innovation And Socially Beneficial Cooperation

Patents do more than create incentives for innovation. By requiring inventors to disclose genetic inventions and enable their use in public filings, patents advance the state of human knowledge, spurring still further innovation. Moreover, because patents offer protection for intellectual property despite (indeed, because of) disclosure, patents also facilitate the collaboration among entities, including potential competitors, necessary to get life-saving products to market.

1. A patent represents "a carefully crafted bargain" in which the patentee is granted "an exclusive monopoly for a limited period of time" in exchange for "the public disclosure" of a new invention. *Pfaff* v. *Wells Elecs., Inc.*, 525 U.S. 55, 63 (1998). The inventor must describe the advance in detail and provide enough information to enable others to practice it themselves. 35 U.S.C. § 112. The inventor also must "set forth the best mode contemplated by the inventor * * * of carrying out the invention." *Id.* § 112(a).

That bargained-for disclosure accelerates innovation at the same time that it protects the patentee's investment in the invention. Requiring full disclosure does not merely ensure that the public will be able to freely use the invention immediately upon the patent's expiration.

It also allows other inventors to build on the work of those who have gone before them. See *Scott Paper Co.* v. *Marcalus Mfg. Co.*, 326 U.S. 249, 255 (1945). The disclosures required by our patent system thus allow everyone to stand on the shoulders of giants (as well as lesser innovators). The USPTO reports that "roughly 90 percent of all pending patent applications are published at eighteen months." FTC, *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy* 26 (Oct. 2003), available at http://www.ftc.gov/os/2003/10/innovationrpt.pdf. Companies utilize that knowledge base to develop further advances that build on the patented technology. See Toneguzzo, 5 Expert Op. Med. Diag. at 275 ("the evidence shows that patents do not inhibit research leading to new discoveries and, in fact, may in some cases stimulate it through the disclosure of innovations").

The requirements that patents contain a detailed description of the invention, enable others to practice the invention, and set forth the best mode of implementing it, make patents particularly powerful tools for the advancement of knowledge. Those seeking to understand the invention do not need to re-invent a hidden or omitted step or detail. Nor do those who seek to understand the optimal implementation of the invention need to waste time and effort reverse-engineering the product or trying to cobble it together using disparate, incomplete sources of public information, such as academic articles.

2. Strong patent protection also permits the establishment of cooperative arrangements necessary to bring life-saving products promptly to market—arrangements that might otherwise prove impossible. For example, the first semi-synthetic penicillins like ampicillin—critical to overcoming staphylococci resistant to biological penicil-

lins—owed their development and their prompt availability to strong patent protection. See Taylor & Silbertson, *The Economic Impact of the Patent System* 258-259 (1973). Developed by a British company, ampicillin held life-saving potential for numerous applications. But the innovator lacked experience in large-scale pharmaceutical manufacturing. It therefore partnered with a more experienced American pharmaceutical company to develop manufacturing techniques, exchanging information and licenses. *Id.* at 258. "[H]ad effective sole patent protection been unavailable in the U.S.A.," however, "it would have been extremely difficult to persuade [the American manufacturing expert] to divulge its manufacturing know-how" in return for distribution rights, delaying or even imperiling the life-saving antibiotic's global distribution. *Id.* at 259.

Today, the field of "companion diagnostics" provides a similar example of how patent protection fosters life-saving cooperation. Through companion diagnostics, personalized medicine utilizes genetic testing to identify from the outset which treatments will benefit a patient and which will not. See FDA, *Draft Guidance* 6-7. Companion diagnostics thus permits treatments that are custom-tailored to a patient's unique genetic profile, preventing the needless suffering and wasteful spending that results when a patient tries drug regimens that do not work for her.

The development and commercialization of companion diagnostics, however, requires collaboration, including the sharing of clinical samples, data, and other information among various industry participants. For example, Roche and Abbott Laboratories together made one of the first significant advances in this area, leveraging the power of a companion diagnostic in connection with Herceptin® (trastuzumab). *See* PricewaterhouseCoopers LLP, *The New Science of Personalized Medicine: Translating the Promise into Practice* 7 (Oct. 2009). Herceptin® is a drug developed by Roche's affiliate Genentech, Inc., to treat a particularly aggressive form of breast cancer. Although only a small portion of those suffering from breast cancer will benefit from Herceptin®, for that subpopulation the drug is extraordinarily effective, increasing survival periods by an average of 25%. It is also highly effective in lowering the risk that early-stage breast cancer will return. *Ibid.*

Because of personalized medicine, Herceptin® treatment can now be targeted to the subset of the population for whom it has that life-saving and life-extending potential. Abbott developed and commercialized the first diagnostic test to identify those patients who exhibit overexpression of a protein known as human epidermal growth factor receptor type 2 ("HER-2") due to a genetic anomaly. That overexpression of the HER-2 protein is associated with certain particularly aggressive cancers. Most importantly, it also predicts whether the patient will have a dramatic response to treatment with Herceptin®. Thus, HER-2 companion diagnostics not only identifies patients who will respond to Herceptin®, it also helps identify patients who will not, avoiding the costs and life-threatening delays associated with unnecessary Herceptin® treatment. See Hillner & Smith, *Do the Large Benefits Justify the Large Costs of Adjuvant Breast Cancer Trastuzumab?*, 25 J. Clinical Oncology 611, 612 (2007); see generally Dendukuri *et al.*, *Testing for HER2-positive Breast Cancer: A Systematic Review and Cost-Effectiveness Analysis*, 176 Can. Med. Ass'n J. 1429 (2007). Herceptin® and its companion diagnostic tests for HER-2 have had a major impact in the treatment of cancer, including metastatic breast cancer. See Tan & Swain, *Ongoing Adjuvant Trials with Trastuzumab in Breast Cancer*, 30 Seminars in Oncology 54, 54 (2002). The development of companion diagnostics for Herceptin® thus illustrates the success of personalized medicine and the promise it holds for the future of the health-care industry.

Absent patent protection, some companies might resist the kinds of collaboration that enable such advances in companion diagnostics for fear that competitors will appropriate their technology without compensation and undercut them in the market because the competitors do not have the same research and development costs to recoup. The disclosures and exchange of information underpinning industrial cooperation and the development of collaborative technologies such as companion diagnostics would be squelched.

3. Patents also permit universities and nonprofit research institutions to maximize their impact on public health through partnerships with private industry.

Such partnerships have proven critical in the fight against cystic fibrosis, a genetic disorder that afflicts approximately 30,000 Americans. The University of Michigan, Johns Hopkins, and the Hospital for Sick Children in Toronto, Canada all hold patents covering DNA sequences relating to and methods of detecting mutations of the *CFTR* gene, which causes cystic fibrosis. Chandrasekharan *et al.*, *Impact of Gene Patents and Licensing Practices on Access to Testing for Cystic Fibrosis* 5-6 (2010) ("*Cystic Fibrosis Study*"), in Secretary's Advisory Comm. on Genetics, Health, & Soc'y, HHS, *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests* (2010) ("SACGHS Report"). By granting non-exclusive licenses for their patents, they spawned a multitude of diagnostic kits for cystic fibrosis: Luminex has created and received FDA approval for its Tag-It cystic fibrosis diagnostic kit, which tests for 39 mutations and 4 variants of the *CFTR* gene. *Id.* at 7-8. And several other manufacturers have "prepar[ed] FDA approved diagnostic tests to compete in the CF testing and screening markets," including Nanogen and Third Wave (subsequently acquired by Hologic). *Ibid.*

None of those tests would have been possible absent the patented discoveries licensed to the companies by the University of Michigan, Johns Hopkins, and the Hospital for Sick Children. The cystic fibrosis example thus illustrates how "patenting and licensing decisions" may "allow for significant research" of a gene and its mutations "without unduly hindering patient access or commercial markets. These practices also preserve strong patent protection and the accompanying investment incentives for possible therapeutic discoveries arising from the same DNA patents." *Cystic Fibrosis Study* 21.

The experience of the Wisconsin Alumni Research Foundation ("WARF") is similar. WARF has developed a program to license its patents broadly on a non-exclusive basis. WARF, *Licensing Process*, http://www.warf.org/industry/index.jsp?cid=1. It seeks out partnerships with any company that:

- "sees the likely commercial benefit to itself of one of WARF's technologies developed at the [University of Wisconsin]-Madison";
- "has the capability to develop early-stage technology (typical of university research) and is willing to make a reasonable effort to commercialize it";

- "is able to demonstrate its serious intent by paying a reasonable licensing fee and reimbursing patent costs associated with the technology"; and
- "is willing to share some of the benefits of the commercial use of the technology with WARF and the UW-Madison through payment of a reasonable royalty on product sales."

Ibid. WARF "shares in the development risk by requiring a reasonable license fee and a royalty that is received only after a product or process is being sold or otherwise used." *Ibid.* WARF's broad licensing practices generate significant revenue—over $54 million in 2008 alone. *Licensing Revenue 2008*, OnWisconsin Magazine, http://onwisconsin.uwalumni.com/departments/licensing-revenue-2008. But WARF benefits in other ways as well, attracting "additional 'margin of excellence' research funding to the UW-Madison," and knowing that "the inventions of the UW-Madison faculty" will be put "to work for the maximum benefit of society." WARF, *Licensing Process*, http://www.warf.org/industry/index.jsp?cid=1.

For example, a WARF subsidiary (WiCell Research Institute) broadly licenses its stem cell lines, fulfilling over 900 stem cell licenses since 1999 and shipping stem cells to more than 500 researchers around the world. WARF News, *United States Patent And Trademark Office Upholds Key WARF Stem Cell Patent* (Feb. 28, 2008), http://www.warf.org/news/news.jsp?news_id=224. Those licenses have allowed pharmaceutical companies, research entities, and universities to rely on stem cell technology to devise new ranges of therapies that would otherwise be inaccessible to the public.

WARF's non-exclusive licensing practices have also spawned numerous start-ups to commercialize UW-

Madison's patents. In the field of genetic research alone, those start-ups include LifeGen Technologies LLC (acquired by Nu Skin Enterprises Inc.), Mirus Bio LLC (acquired by Roche), NimbleGen Inc. (also acquired by Roche), and Third Wave Technologies (acquired by Hologic). WARF, *WARF Startups*, http://www.warf.org/startups/index.jsp?cid=44. WARF's experience is yet more proof that, far from hindering innovation in the field of genetics, patents actually spur innovation and benefit the public.

III. PETITIONERS' AND THEIR *AMICI'S* POLICY ARGUMENTS ARE MISPLACED

Petitioners and *amici* assert a host of policy-based arguments that, they contend, counsel against finding isolated DNA to be patentable subject matter under Section 101. They assert that patents on isolated DNA stymie further research and innovation on the genes at issue. See, *e.g.*, Pet Br. 42. They complain that patents on isolated DNA grant patentees rights in applications of the DNA beyond those disclosed in the patent. See *id.* at 41; Br. of AARP 7-8; Br. of Prof. Eileen M. Kane 25. And they claim that isolated DNA patents restrict patient access to life-saving genetic diagnostic tests. *Ibid.* These arguments are overblown as a doctrinal matter—well settled patent-law principles beyond Section 101 already directly address each of those purported concerns. It is thus not surprising that those concerns are also belied by the empirical evidence. The PTO has been issuing patents on isolated DNA for over 30 years, yet there is scant evidence that the problems about which petitioners and *amici* warn have materialized. This Court should not distort the Section 101 analysis in the name of solving problems that do not exist.

A. Requirements Other Than Subject Matter Patentability Appropriately Limit The Scope And Preemptive Effect Of Gene Patents

Petitioners invoke patent policy in support of narrowing the scope of patentable subject matter under Section 101. "The § 101 patent-eligibility inquiry," however, "is only a threshold test" in patentability analysis. *Bilski*, 130 S. Ct. at 3225. That limited test should not be treated as a panacea for all concerns relating to the scope and preemptive reach of isolated DNA patents. Other well settled patent law doctrines already address the issues petitioners raise, properly balancing the interests this Nation's patent laws seek to protect.

The Hatch-Waxman Act Safe Harbor. Petitioners contend that Myriad's patent on isolated DNA gives it "the authority to prevent all study" of "the two human genes," *i.e.*, native BRCA1 and BRCA2. Pet. Br. 42. But Myriad has no such "authority." As a scientific matter, isolating DNA is not "a necessary step" in researching native genes. *Id.* at 41. A variety of non-infringing technologies are available to study DNA or detect genetic mutations without isolation. See Resp. Br. 47. And petitioners are also incorrect as a legal matter. In the Hatch-Waxman Act, Congress specifically carved out a safe harbor from infringement for research and other activities "reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." 35 U.S.C. § 271(e)(1). The exemption provides "wide berth for the use of patented drugs [and other inventions] in activities related to the federal regulatory process." *Merck KGaA* v. *Integra Lifesciences I, Ltd.*, 545 U.S. 193, 202 (2005). Congress thus specifically authorized companies to conduct research to develop new products that might otherwise infringe a patent, and pursue federal regulatory approval of those products, during the patent's exclusivity period so that they may be ready to begin commercial sale as soon as the patent expires. See H.R. Rep. No. 98-857, at 45-46 (1984).

Written Description. Nor can proper patents for isolated DNA "undermine the patent system" by giving the patentee "the right to any applications of isolated DNA without disclosing them." Pet. Br. 41. Section 112's written description requirement prohibits just that. Section 112 requires that the specification contain a "written description of the invention * * * in such full, clear, concise, and exact terms as to enable any person skilled in the art * * * to make and use the same." 35 U.S.C. § 112(a). That requirement ensures (among other things) that patentees adequately describe their inventions in the patent's specification in exchange for the right to exclude others from practicing the invention. See *Bonito Boats, Inc.* v. *Thunder Craft Boats Inc.*, 489 U.S. 141, 150 (1989) ("The applicant * * * who is willing to reveal to the public the substance of his discovery * * * is granted 'the right to exclude others from making, using or selling the invention throughout the United States'" for a certain period.). It thus enshrines a "delicate balance" between the benefit to the public of the invention's disclosure, and the interest of the inventor in protecting the invention. *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 731 (2002).

Petitioners insinuate (at 41) that Myriad's claims exceed what the inventors had discovered when they filed their patent application. The written description requirement prevents such overreaching claims. The very "purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." *Amgen Inc.* v. *Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1330 (Fed. Cir. 2003). A patentee has no claim for infringement on an invention that is not disclosed.

Enablement. Petitioners contend (at 41) that isolated DNA patents improperly grant exclusive rights over all uses of a gene, "including future uses not yet * * * technically achievable." But that argument is foreclosed by Section 112's "enablement" requirement. Under it, the specification must describe the invention in sufficient detail to enable a person skilled in the art "to make and use the full scope of the claimed invention without undue experimentation." *Genentech, Inc.* v. *Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir.) (quotation marks omitted), cert. denied, 522 U.S. 963 (1997); see also *Minerals Separation, Ltd.* v. *Hyde*, 242 U.S. 261, 271 (1916). In evaluating enablement, courts look to the breadth of the claims and the existence of working examples at the time of filing the patent application. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The specification must enable the use of the *full scope* of the claims. *MagSil Corp.* v. *Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012). If a patentee attempted to extend its claims to forms or applications of isolated DNA that were not "technically achievable" at the time of the application, those claims could be invalidated on enablement grounds. Petitioners' concerns are therefore addressed by existing patent law.[6]

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[6] That is not to suggest that Section 112 (or other provisions of the Patent Act) may "substitute" for the patentable-subject-matter inquiry under Section 101. *Mayo Collaborative Servs.* v. *Prometheus*

B. Empirical Evidence Shows That Gene Patents Do Not Impede Research Or Patient Access To Genetic Testing

Historical experience likewise contradicts petitioners' and their *amici*'s claim that, unless the Court restricts Section 101's scope to exclude isolated DNA from patent-eligibility, patentees will impede scientific progress by preventing study of related genomic material, Pet. Br. 42, and restrict patient access to genetic testing, see, *e.g.*, Br. of AARP 7-8; Br. of Prof. Eileen M. Kane 25. Indeed, while petitioners and their *amici* rely heavily on the 2010 SACGHS Report to support their argument that genetic patents impede scientific research and patient access, the empirical case studies underlying the report refute those assertions.

1. Notwithstanding petitioners' and their *amici*'s repeated invocation of the SACGHS Report, *e.g.*, Pet. Br. 42-43, 44; Br. of Int'l Ctr. for Tech. Assessment, *et al.* 17, the studies underlying the SACGHS Report refute their claims. While the SACGHS Report voiced concern that patents *theoretically* could restrict genetic research and development, it conceded that, in reality, the "empirical research suggest[s] that research is not hampered" by patents. SACGHS Report 88. Indeed, the case studies on which the SACGHS Report purports to base its recommendations repeatedly conclude that patents have *not* inhibited follow-on research:

- "Concerns regarding inhibition of research due to the *HFE* gene patents do not seem to be sup-

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Labs., Inc., 132 S. Ct. 1289, 1304 (2012). No provision of the Patent Act, alone or in concert with any other doctrine, justifies the issuance of a patent over a composition of matter that is not a product of human innovation. But isolated DNA clears that threshold requirement. See pp. 5-12, *supra*.

ported. Substantial basic research, including identification of genes and mutations associated with other types of hemochromatosis has continued. Similarly, research on improved methods for detection of *HFE* mutations has also progressed." Chandrasekharan *et al.*, *Impact of Patents and Licensing Practices on Access to Genetic Testing for Hereditary Hemochromatosis* 3 (2009) ("*Hemochromatosis Study*") (SACGHS Report at app. A, pt. E).

- "We have not found any evidence that CF gene patents impeded subsequent basic or clinical research." *Cystic Fibrosis Study* 20.
- "There is no evidence that patents have had a positive or negative impact on hearing loss genetics research." Chandrasekharan & Fiffer, *Impact of Patents and Licensing Practices on Access to Genetic Testing for Hearing Loss* 4 (2009) ("*Hearing Loss Study*") (SACGHS Report at app. A, pt. D).
- "[W]e have no evidence that the virtual LQTS monopoly from 2003-2008 has had any stifling effect on research * * *." Angrist *et al.*, *Impact of Patents and Licensing Practices on Access to Genetic Testing for Long QT Syndrome* 24 (2009) ("*LQTS Study*") (SACGHS Report at app. A, pt. F).
- "[No] evidence of a chilling effect in the basic science arena for either FAP or HNPCC." Cook-Deegan *et al.*, *Impact of Patents and Licensing on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers to Colon Cancer* 27 (2009) ("*Breast, Ovar-*

ian, and Colon Cancers Study") (SACGHS Report at app. A, pt. A).

- "[N]ot f[inding] patents to be a significant impediment to research on [Alzheimer's Disease.]" Skeehan *et al.*, *Impact of Patents and Licensing Practices on Access To Genetic Testing for Alzheimer's Disease* 14 (2009) ("*Alzheimer's Study*") (SACGHS Report at app. A, pt. B).
- "It is clear that the Tay-Sachs gene patent did not stifle research as it was never enforced. * * * [T]hough the Canavan patent could in theory have impeded research until 2003, it does not anymore." Colaianni *et al.*, *Impact of Patents and Licensing Practices on Access to Genetic Testing and Carrier Screening for Tay-Sachs and Canavan Disease* 14 (2009) ("*Tay-Sachs and Canavan Study*") (SACGHS Report at app. A, pt. H).

A committee of Australia's Senate specifically studied Myriad's patent and licensing practices for BRCA1 and BRCA2 in that country and concluded that "patents over human genes and biological materials have not hindered research, particularly medical research, in Australia." Legal and Constitutional Affairs Legislation Comm., *Report on Patent Amendment (Human Genes and Biological Materials) Bill* 62 (2011), available at http://www.aph.gov.au/Parliamentary_Business/Committees/Senate_Committees?url=legcon_ctte/completed_inquiries/2010-13/patent_amendment/report/report.pdf.[7] To the contrary, the report found, "patents have encouraged and contributed to research and development activities" because "[p]atents allow researchers to attract investment to pursue the development of new inventions and allow companies to mitigate the risk associated with developing costly new products." *Ibid.*[8]

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[7] The assertion that Myriad's BRCA1/2 patents stifle study of those portions of the human genome is further belied by the number of published academic studies on BRCA1/2 during the life of Myriad's patents. Petitioners and their *amici* cite more than a dozen.

Numerous other studies focused on the effect of gene patents have reached similar conclusions: "[T]he evidence shows that patents do not inhibit research leading to new discoveries and, in fact, may in some cases stimulate it through the disclosure of innovations." Toneguzzo, 5 Expert Op. Med. Diag. at 275; see generally Caulfield, *Human Gene Patents: Proof of Problems?* 84 Chi.-Kent L. Rev. 133, 135-139 (2009) (reviewing numerous studies and finding no evidence of constraints on research). A 2005 survey of scientists involved in biomedical research likewise found that "patenting does not seem to limit research activity significantly, particularly among those doing basic research." Walsh *et al.*, *Patents, Material Transfers and Access to Research Inputs in Biomedical Research* 3 (Sept. 20, 2005) ("Walsh, *Patents & Access*"); see also Walsh *et al.*, *View From the Bench*, 309 Science 2002 (2005). And an earlier study found that patents "rarely precluded the pursuit of worthwhile projects." Walsh *et al.*, *Working Through the Patent Problem*, 299 Science 1021, 1021 (2003). When requested, licenses were often available at minimal or no cost. Walsh, *Patents & Access* 17. "Thus, not only are barriers or delays rare, but costs of access for research purposes are negligible." *Ibid.*

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[8] The Federal Court of Australia recently upheld the validity of Myriad's BRCA1 and BRCA2 patents in that country. *Cancer Voices Australia* v. *Myriad Genetics, Inc.* [2013] FCA 65 (Austl.).

2. Nor does the SACGHS Report support the contention, Br. of AARP 7-8; Br. of Prof. Eileen M. Kane 25, that gene patents prevent patients from accessing genetic testing. A passage cited by the AARP does suggest that some patients seeking BRCA testing have been unable to do so due to "Myriad's decision not to accept particular insurers." SACGHS Report 43. But the only relevant "evidence" cited by the Report for that assertion are *allegations in the complaint in this case*. See *id.* at 43 & n.118, 44 & n.120. Allegations in a complaint are not evidence; and the Report cites nothing more to support any such assertions.

Meanwhile, the rigorously documented case study on BRCA testing attached to the SACGHS Report sharply undercuts any suggestion that it was Myriad's patents that impeded patient access. Instead, any problems appear to have resulted from the insurance industry's failure to respond to medical progress with sufficient alacrity:

- "[C]overage and reimbursement practices of insurers and other payers are crucial. * * * [I]nsurance companies are slow to respond to claims for genetic tests * * * ." *Breast, Ovarian, and Colon Cancers Study* 31.
- As of late 1995—the year that Myriad filed applications for the patents at issue here—"only 4% of insurance providers * * * had granted coverage of BRCA testing." *Id.* at 37. But, by 2008, "Myriad ha[d] established contracts or payment agreements with over 300 carriers and ha[d] received reimbursement from over 2500 health plans." *Id.* at 32.

- Insurers now cover "roughly 95% of those requesting tests, and reimburse[ ] to cover 90% of their charges." *Id.* at 37.

The facts gathered in the case study refute *amici's* counter-intuitive charge that Myriad would refuse insurance dollars and sabotage widespread utilization of BRCA testing in the process.

Even beyond the BRCA-specific case study, the SACGHS Report refuted efforts to blame patient-access problems on patent protection. It found no evidence of access issues being caused by patents (as opposed to insurance coverage), even where patents are exclusively licensed. And it observed that "the case studies generally found that for patented tests that were broadly licensed"—a common industry practice favored by most major innovators—"there was *no evidence* of patient access problems." SACGHS Report 42 (emphasis added). Indeed, the SACGHS-commissioned study on cystic fibrosis found "no evidence that patents have significantly hindered access to genetic tests." *Cystic Fibrosis Study* 2. Another study found that "[p]atents do not appear to have significantly impeded patient or clinical access for hearing loss genetic testing." *Hearing Loss Study* 26. And the study on genetic testing for hemochromatosis found that "testing is widely available from multiple sources," and that there is "little evidence bearing on the impact of patents on consumer utilization." *Hemochromatosis Study* 4, 5.[9]

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[9] Indeed, the SACGHS Report identifies only *one potential* example of exclusively licensed patents restricting patient access—LQTS testing. There, based on evidence that was "acknowledg[ed]" to be "incomplete," SACGHS Report 42, a study concluded that "access problems *may* have occurred * * * during an 18-month period due to patent enforcement," "*if* there were patients seeking the test at that

Alarmist rhetoric should not obscure the empirical evidence. For 30-plus years, the PTO has granted patents on isolated DNA. See Pet. App. 61a. But the parade of horribles petitioners and their *amici* posit has not come to pass. Narrowing Section 101's scope to exclude man-made isolated DNA, by contrast, would threaten investment and medical progress at this critical juncture. This Court has previously made clear that it "is without competence to entertain" policy-based pleas to limit the scope of Section 101: "Whatever their validity, the contentions now pressed on [the Court] should be addressed to the political branches of the Government, the Congress and the Executive, and not to the courts." *Chakrabarty*, 447 U.S. at 317. Because isolated DNA meets the requirements for patentable subject matter, it should be patentable. Petitioners' theory that gene patents are too important or too basic a building block to be patented is, at this late date, better addressed to the political branches.

CONCLUSION

The judgment of the Federal Circuit should be affirmed.

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time," but "[w]hether there were such patients is not documented," *id.* at 44 (emphases added). The one example the SACGHS Report could muster—"incomplete" evidence showing patients "may" have had access problems "if" any patients existed at all—does not establish that even exclusive licensing of patents has restricted patient access, much less caused a significant problem or actual health effects.

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MARCH 2013

AMICUS
CURIAE
BRIEF

No. 12-398

Supreme Court, U.S.
FILED
MAR 14 2013
OFFICE OF THE CLERK

IN THE

Supreme Court of the United States

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On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

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BRIEF FOR *AMICUS CURIAE* CROPLIFE INTERNATIONAL SUPPORTING RESPONDENTS

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QUESTION PRESENTED

As they occur in nature, biologics (such as genes) exist in complex milieux. They are intimately and inherently associated with a wide range of other naturally-occurring materials. Biologics can be presented in isolated forms, but only through human handiwork and intervention. These "isolates" are freed from other cellular materials. Isolates are therefore capable of exploitation for the betterment of humankind in innumerable desired, controlled, and often novel ways, none of which are ever seen in nature.

Given the foregoing, should biological isolates be considered new and useful compositions of matter that are distinct from their naturally-occurring counterparts and, therefore, eligible for patent protection under 35 U.S.C. § 101?

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BRIEF OF *AMICUS CURIAE* CROPLIFE INTERNATIONAL SUPPORTING RESPONDENT

INTEREST OF *AMICUS CURIAE*[1]

CropLife International (CropLife) is a global federation representing the plant science industry and a network of regional and national associations in 91 countries. CropLife also has company members, including BASF,

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[1] Pursuant to this Court's Rule 37.6, *amicus* affirms that no counsel for a party authored this brief in whole or in part, that no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief, and that no person or persons other than *amicus* and its counsel made such a monetary contribution. Petitioners' consent to the filing of all *amicus* briefs is on file with the Clerk's office and respondents' consent to the filing of this brief was obtained from respondents' counsel on February 25, 2013 by e-mail correspondence, which is being lodged with the Clerk.

Bayer CropScience, Dow AgroSciences, DuPont Pioneer, FMC, Monsanto, Sumitomo, and Syngenta. These companies are committed to sustainable agriculture through innovative research and development in the areas of crop protection, pest control, and seed and plant technologies.

The innovations provided by CropLife member companies include, or are based on, isolated biologics, including isolated DNA molecules, cultures of isolated microorganisms, and other isolated substances found in nature. For example, isolated DNA molecules are used to bioengineer plants to have one or more novel properties, while cultures of isolated microorganisms are used, *e.g.*, as biocontrols to protect plants from various forms of pathogen infestation. With access to biologics such as these, crop yields increase and our dependence on pesticides, herbicides, water, and nutrients decreases. This benefits the environment, farmers, and the public. Consumers benefit too; they receive access to crop-based foods that, *e.g.*, are richer in nutrients or exhibit other salutary features. Plants engineered for increased production (of products like foods, oils, and fibers) and for decreased dependence on scarce resources (*e.g.*, water), are of self-evident benefit. This is especially true in countries experiencing deprivation. To recoup the investments made in these research and development efforts, CropLife's member companies rely on the exclusivity afforded by patents, including patents on isolated DNA molecules and other substances having counterparts in nature.

SUMMARY OF ARGUMENT

This case is about *patent-eligibility* under §101, not patent validity under other sections of the Patent Act. This Court has recognized § 101's breadth, characterizing it as reaching "anything under the sun that is made by man." *Diamond* v. *Chakrabarty*, 447 U.S. 303, 309 (1980) (internal quotations omitted). Myriad's claims easily satisfy that standard. Other concerns regarding those claims' validity, even if possibly meritorious, are irrelevant here; all that has been litigated, and all that this Court should decide, is whether their subject matter is patent-eligible.

1. Myriad's claims cover "isolates" of particular human genes. These are man-made versions of genes that are freed from the cellular components that associate with genes as they exist in humans. Nothing about Myriad's claims (or claims to any other biological isolate) attempts to cover nature's handiwork. Although this case formally focuses upon isolates of *human* genes, the reason that Myriad's claims satisfy § 101 also applies to any type of biological isolate, be it a non-human gene, another substance (such as a protein or an antibiotic), or a microorganism.

2. The patent-eligibility of biological isolates has generated extraordinary benefits to society. The isolated BRCA genes at issue here represent one end of the spectrum of biologics. They can save or sustain the lives of women predisposed to breast or ovarian cancer, typifying the "personalized medicine" revolution occurring in health care. Isolates of microbial origin, at the other end of the spectrum, are likewise revolutionizing agriculture, and thereby generating more for the world's people, at lesser cost, with higher quality, and often with substantial environmental benefits. Isolated versions of microbial genes can confer on plants desirable traits that they do not naturally possess, such as enhanced flavor, higher nutritional value, or the capacity to withstand adverse conditions, both before and after harvest. Such inventions have considerably improved agricultural development, and have even saved some staples—like the Hawaiian papaya—from extinction.

The benefits of biological isolates are extraordinary, and the short summary provided here understates their scope and import. Their patent-eligibility is what has spurred those in the agricultural sector—and in other sectors—to make the investments necessary to create these new developments.

Whether to strip isolated biologics of patent-eligibility is, therefore, a policy question of great importance. But it is one for Congress, which is well aware of their being patented; it has chosen, however, only to eliminate patent-eligibility for a "human organism," and has rejected proposals to deny patent-eligibility to any other biologic. Any further changes to the standards of patent-eligibility should come from Congress, not the courts.

3. The posture of this case—arising with a scant summary-judgment record—also justifies caution. The Court should reject petitioner's attempt to introduce highly contested "evidence" that isolated versions of the BRCA genes *do* exist in nature.[2] No source supports this assertion, and logic refutes it; human genes in nature, unlike Myriad's isolates, are invariably associated with additional cellular components.

Similarly, petitioner tries to smuggle a question more properly addressed by § 112 into this § 101 case—he claims that Myriad's claims are too broadly written. And he attempts to solicit this Court in an extra-*Markman* claim-construction exercise, arguing theories about the claims' scope that improperly and unfairly distort the legal question before the Court. Because these issues were not litigated below, they should be ignored in favor of a case that properly presents them and, unlike this case, is brought by a petitioner with unquestionable standing.

4. Relying on a series of this Court's cases, petitioner

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[2] Although this case is purportedly brought by multiple "petitioners," only one petitioner (Ostrer) has been held to have adequate standing, and that is tenuous at best. See Pet. App. 41a. Accordingly, *amicus* will describe arguments advanced by the petitioner, in the singular.

seeks to demonstrate why human gene isolates cannot be patent-eligible. But any biological isolate would satisfy the key case, *Chakrabarty*. The other cases relied upon are inapposite, and, if anything, actually favor Myriad. *Funk* dealt with what is now called "obviousness," not patent-eligibility itself, which the Court acknowledged. *American Fruit Growers* dealt with whether a treated citrus fruit qualified as an "article of manufacture," but that has nothing to do with biological isolates, which are "compositions of matter." Finally, this Court's recent decision in *Mayo* does not resolve this case, because Myriad has not patented a natural phenomenon or a law of nature. Its claims only cover genes to the extent they are presented in an *isolated* form, compositions of matter that are otherwise unknown in nature.

ARGUMENT

ISOLATED BIOLOGICS, WHETHER HUMAN GENES OR OTHERWISE, ARE PATENT-ELIGIBLE UNDER § 101

Under *Chakrabarty*, anything that is the product of man's intervention and is distinct from what is found in nature is patent-eligible. This case does not ask whether the claims at issue are valid under all provisions of the Patent Act and across their entire breadth; it simply asks whether they are patent-eligible under 35 U.S.C. § 101 to the extent they cover particular subject matter: isolated genomic and cDNA versions of human genes. Under § 101 and this Court's cases, the answer to that question must be "clearly, yes."

Providing a biologic in an isolated form so that it is freed from the components it inextricably associates with in its natural milieu meets the *Chakrabarty* and, therefore, the § 101, test. Beyond being freed from cellular components they naturally associate with, isolated genes, as a class of biologics, are further distinct from their naturally-occurring counterparts in that they are unique chemical entities, liberated from chromosomes and, hence, freed from the covalent bonds that connect their naturally-occurring counterparts to neighboring chromosomal DNA.

The DNA molecules at issue here, taking the forms of *isolates*, necessarily steer clear of covering genes as they occur in the human body. Neither a DNA molecule nor any other *isolated* biologic is a "natural phenomen[on]." Cf. *Mayo Collaborative Servs.* v. *Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2011). To the contrary, they take a form that does not exist in nature and would not exist at all without man's intervention and handiwork. This Court should affirm the judgment below.

A. This case addresses the patent-eligibility of isolated versions of any biologic, not just isolated human genes

Petitioner frames the issue in this appeal as one concerning the patent-eligibility of isolated versions of *human* genes. See, *e.g.*, Pet. Br. i (question presented), 3, 55. But no logical basis exists for treating these isolates differently from any other kind of biological isolate, at least with respect to the threshold question of patent-eligibility under § 101—they are all equally isolates, and hence distinct, because of man's handiwork. Cf. Resp. Br. 60-61.

The Court should recognize, therefore, that any biological isolate satisfies the basic requirements of § 101. The patent-eligibility of biological isolates—which can range from genomic or cDNA versions of human genes, such as the BRCA genes covered by the claims at issue here, to non-human genes and microorganisms—matters a great deal to our society and to humanity at large. Because the patent-eligibility of many biologics is premised on their isolated state, depriving isolated human genes of patent-eligibility would have cascading negative consequences in many fields beyond health care that rely on the patentability of other types of natural biologics to spur their innovations.

1. Biological isolates are compositions of matter that are never found in nature and only exist through man's handiwork

a. Any biological isolate is a composition of matter that is man-made—that is, one that only comes into existence as a result of man's intervention and handiwork. That is because all biologics are present in nature in an environment that has other naturally-occurring materials present with which they associate. Through intervention and handiwork, man must either: (a) retrieve a sample from nature that harbors the biologic of interest and employ techniques to remove these "naturally-occurring contaminants," or (b) produce the biologic in the laboratory, employing conditions and techniques that ensure that the biologic is freed from such "contaminants," thereby creating something that never exists in nature.

b. A human gene is but one example of a biologic and is the class the petitioner has framed this appeal around. That is because the claims at issue are directed to isolated DNA molecules that contain nucleic acid sequences found in the BRCA genes present in human chromosomes. Petitioner asserts that, since the claims are so broad as to cover all isolated genomic and cDNA versions of these genes, they essentially cover the genes as they exist in human body, which are unpatentable.[3]

c. But the concept of a biologic extends well beyond human genes. It embraces genes from any organism, such as other animals, plants, and from microorganisms, such as bacteria, fungi, and yeast. It also embraces the proteins encoded by genes and microorganisms themselves. Insofar as the agricultural sector is concerned, a sector of particular interest and concern to CropLife's members, a range of innovations have been developed that, at their core, rely on isolated genes from microorganisms and plants (*e.g.*, to impart novel traits to crops) as well as microorganisms themselves (*e.g.*, to serve as inoculants that protect crops from various pathogens). See Section B.2, *infra*.

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[3] Genomic and cDNA versions of the BRCA genes share in common the fact that they both contain the coding sequences for the BRCA proteins. But the two versions differ in that the cDNA version only contains coding sequence, while the genomic version also contains "introns," or non-coding sequences interspersed within the coding sequence. See generally Pet. App. 15a-19a.

d. The Federal Circuit properly held that the claims at issue in this appeal do not impermissibly cover the BRCA genes as they occur in nature. By virtue of being limited to *isolated* DNA molecules—which, through man's intervention, are removed from the cellular milieu in which human genes are found—the claims are directed to molecules that are distinct from the BRCA genes as found in humans. Pet. App. 51a-55a.

2. *The question presented by petitioner implies a limitation—to "human" genes—that law and logic cannot accept*

The springboard for this appeal is a set of claims directed to isolated DNA molecules that collectively cover isolated versions of the human BRCA genes. Given that scope, petitioner has couched the Question Presented as whether such claims are impermissibly covering human genes as they occur in the body. But as demonstrated above, nothing logically distinguishes human genes from other biologics in this context. The Court's decision thus could have a profound impact on a wide range of biologics that are providing innovative solutions in areas outside of health care that are critical to our welfare and survival.

B. Patent-eligibility for biological isolates has generated extraordinary achievements in many contexts

Recognizing the patent-eligibility of isolated human genes fulfills Congress's objective of liberally encouraging human ingenuity. The same is true of all other biological isolates.

1. Human genetic developments, like those in this case, portend a new era of personalized medicine

The isolation of the human BRCA genes, and the identification of specific sub-sequences of these genes as biomarkers for breast and ovarian cancer, represent exactly the kind of human activity and ingenuity contemplated by Congress as meriting patent protection. See *Chakrabarty*, 447 U.S. at 309. These advancements benefit society at large, and could never be made without human intervention and ingenuity. Mutations in these genes are predictive of breast and ovarian cancer in a significant number of humans; being able to employ the claimed DNA molecules to detect these genes, particularly the markers for cancer that they bear, unquestionably saves lives. Indeed, the search for such mutations is so important to human health that it has become a priority for the National Institutes of Health (NIH).[4]

The human BRCA genes were among the earliest human genes to be cloned and identified as carrying markers for cancer. The identification and cloning of these two genes and the mapping of their markers were no small feats and represent true human ingenuity.[5] The

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[4] See, *e.g.*, National Institutes of Health, Fact Sheet—Cancer (2010), available at http://report.nih.gov/NIHfactsheets/Pdfs/Cancer(NCI).pdf.

[5] See, *e.g.*, Miki et al., A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1, 266 Science 66-71 (Oct. 7, 1994), available at www.ncbi.nlm.nih.gov/pubmed/7545954; and Tavtigian et

DNA isolates disclosed and claimed by Myriad, which include genomic and cDNA versions of the BRCA genes, enable testing for these markers in high-risk patients, which has become the standard of care in the medical profession.[6]

It is all too easy to breezily suggest that claims like those at issue are not patent-eligible because they impermissibly cover natural phenomena. After all, the DNA molecules claimed cover isolated versions of human genes found in nature. But the discovery of such genes, their relationship to disease (*e.g.*, cancer), and their utility in diagnosing and treating disease represents a critical advance in the important art of making those predisposed to developing diseases healthy. Where a tool for identifying those who are at risk of developing a disease is discovered, it represents a true advance in the art of medicine and technology. Moreover, as reflected in Section D.1.b, below, when a claim clearly calls for a DNA molecule as an "*isolate*," such claim language should suffice to render the claimed subject matter patent-eligible under § 101—even if it extends to covering isolated versions of a human gene.

2. Biological isolates being developed and patented in the agricultural sector confer useful traits to plants and are important to plant cultivation

The discovery, development, use, and patenting of biological isolates is extensive. It extends far beyond human

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al., The complete BRCA2 gene and mutations in chromosome 13q-linked kindreds, 12 Nat. Genet. 333-337 (Mar. 1996), available at www.ncbi.nlm.nih.gov/pubmed/8589730.

[6] See, *e.g.*, Biesecker et al., Genetic counseling for families with inherited susceptibility to breast and ovarian cancer, 269 Journal of the American Medical Association 1970-1974 (No. 15, Aug. 18, 1993), available at www.ncbi.nlm.nih.gov/pubmed/8352830.

genes useful for cancer diagnostics. Indeed, some of the most important isolates, and those of particular interest and concern to CropLife's members, are of microbial origin, consisting of isolated bacteria, fungi, viruses, and genes derived from them. The range is remarkably wide, but at each point throughout the range, these isolates provide innovative and often environmentally-friendly solutions to meeting many of society's most basic needs. These biologics are helping, and, if not impeded, will continue to help, feed, fuel, and clothe our ever-expanding population, which has reached, or soon will reach, seven billion.[7]

Various isolated versions of microbial and plant genes have been used to confer desirable traits on crops. In addition, genetic DNA markers have been identified in plants that can be used to select crops, produced through selective breeding techniques, possessing certain traits. The range of traits genetically engineered into plants includes enhanced flavor, higher nutritional value, longer shelf-life, and resistance to various conditions, such as drought, extreme heat or cold, and herbicide and pesticide treatment.[8] The list of plants modified with such traits includes important food staples, such as soybeans, tomatoes, corn, canola, squash, potatoes, alfalfa, papayas, and sugar beets, as well as fiber-producing plants such as cotton.

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[7] See Soils, Society & Global Change, Proceedings of the International Forum Celebrating the Centenary of Conservation and Restoration of Soil and Vegetation in Iceland 53 (2007), available at http://eusoils.jrc.ec.europa.eu/esdb_archive/eusoils_docs/other/EUR 23784.pdf.

[8] See, *e.g.*, the following patents, claiming the following gene isolates: U.S. Patent No. 7,947,867 (USDA) (a DNA molecule that can increase a fruit's shelf-life); U.S. Patent No. 7,932,434 (USDA/ WARF) (a polynucleotide that can confer disease resistance to solanaceous plants); U.S. Patent No. 7,439,419 (USDA) (a nucleic acid molecule that can reduce the bitter taste of certain vegetables); U.S. Patent No. 8,278,505 (Dow AgriSciences) (a polynucleotide that can confer herbicide-resistance to plants); U.S. Patent No. 8,299,324 (Bayer Cropscience N.V.) (DNA that can confer insect-resistance to plants).

These innovations, which depend on the ability to identify and isolate non-human genes and use them to impart novel traits to plants, generate exceptionally beneficial consequences. As one concrete example, this ability essentially saved the papaya, a key Hawaiian export, from extinction there. Papaya is a subtropical-tropical fruit grown year-round in Hawaii. Rich in both vitamins A and C, it is a healthy staple for many worldwide. But in 1992, Papaya ringspot virus (PRSV) broke out in Hawaii and, within six years, ravaged production to the point that the annual papaya yield was less than half its pre-1992 level. See Biotechnology Industry Organization, Healing, Fueling, Feeding: How Biotechnology Is Enriching Your Life 66-67 (2010) ("Healing, Fueling").[9]

Salvation for the Hawaiian papaya came from isolating the gene that encoded the virus's coat protein and using that isolate to create a PRSV-resistant papaya. See Healing, Fueling, *supra*, at 67. Cornell University and the University of Hawaii jointly performed this work and hold a patent relating to this technology, which claims an isolated nucleic acid molecule encoding the PRSV coat protein—indistinguishable for legal purposes from the claims at issue in this case. See U.S. Patent No. 7,553,668. With the benefit of the resistance conferred by the PRSV coat protein gene, papaya is the second largest fruit crop grown in Hawaii. See Healing, Fueling, *supra*, at 67.

Our country's dependence on isolated genes to modify crops is even more extensive than the foregoing example might suggest. As of 2009, over 158 million acres were devoted to cultivating not only genetically-modified papayas, but also soybeans, maize, cotton, canola, squash, alfalfa, and sugar beets, making the United States the world's top producer of genetically-modified crops. See Healing, Fueling, *supra*, at 57, Fig. 3.

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[9] Available at http://www3.bio.org/news/publications/ValueofBiotech.pdf.

The isolation of non-human genes and genetic modification of crops with such genes play prominent roles in the "green revolution," which has enabled farmers to increase their crop yields while simultaneously reducing the environmental footprint of their activities. Indeed, between 1992-2008 alone, the use of genetically-modified crops translated into a 352 million-pound reduction in the amount of herbicide and pesticide used to treat crops. See Healing, Fueling, *supra*, at 78. See also CropLife International's *amicus* brief to the Federal Circuit in this case, at 14 (highlighting how environmentally-unfriendly tilling practices have been significantly reduced with the use of genetically-modified crops).

Genetically modifying plants and seeds is not the only way those active in the agricultural sector are meeting society's basic needs. They are also developing and patenting inoculants, akin to those featured in *Funk*, that rely on, *e.g.*, isolated cultures of microorganisms to stimulate crop growth, augment crop yields, and combat various forms of infestation.[10] Hundreds of such biologics are currently in use just in North America. See http://www.cdpr.ca.gov/docs/pestmgt/ipminov/bensup.pdf.

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[10] See, *e.g.*, the following patents claiming isolated microorganisms: U.S. Patent No. 6,210,953 (U. Wy./AGERI) (strains of the bacterium *Bacillus thuringiens* for use as pesticides); U.S. Patent No. 7,001,755 (USDA/OURF) (strain of the bacterium *Bacillus sp.* NRRL B-30212 to prevent head blight caused by fungi); U.S. Patent No. 7,579,183 (USDA) (strain of the yeast *Pichia anomala* for controlling various types of bacterial and fungal pathogens); U.S. Patent No. 5,955,348 (Novartis AG) (strain of the bacterium *Pseudomonas fluorescens* for treating various fungal pathogens).

This survey is, of course, grossly abbreviated. But it leaves little room for doubt that biological isolates in the agricultural sector are providing enormous benefits to the public.

3. Patent protection for such innovations spurs investment in these developments

Those active in the agricultural sector expend hundreds of millions of dollars annually, paying for a massive workforce to research, develop, market, and sell innovative products like those described above. The potential to secure patent protection for these new developments is a chief means for recouping those investments and ensuring that innovations are brought to the public. Patent-eligibility provides a key incentive for agricultural concerns to hire employees and expend the time, energy, and resources necessary to bring valuable innovations to market. Put simply, patented isolated biological compositions of matter stimulate the economy and create American jobs.

The United States Government certainly recognizes this in its own practices. The promise of patent protection has incentivized federal agencies, like many universities, to bring about the very types of innovations described above. Recognizing that such patent estates can provide significant royalty streams, the U.S. Department of Agriculture has devoted an entire webpage to promoting the out-licensing of its own patent holdings in this field.[11] Indeed, the bulk of the patents listed in footnotes 8 and 10, *supra*, are held by governmental or educational institutions, not by corporations.

Hence, this Court's holding has the potential to either advance or hinder the discovery and development of, and the public's access to, extraordinary new inventions of tremendous social, economic, and environmental value.

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[11] *E.g.*, http://www.ars.usda.gov/business/docs.htm?docid=763&page=5; http://www.ars.usda.gov/business/docs.htm?docid=763&page=5.

4. Congress has already indicated which biologics should be patent-eligible; if patent-eligibility requires further modification, that is a policy matter for Congress

The Constitution endows Congress with the authority and responsibility to enact laws that promote "Science and useful Arts." U.S. Const. art. I, § 8, cl. 8. Over more than two centuries, Congress has enacted various patent acts that define what subject matter is eligible for patent protection. When Congress has deemed man's acts of ingenuity to come too close to nature's own handiwork, or, for some other reason, to be improper as a policy matter, it has limited the scope of subject matter eligible for protection—but not by banning the patenting of all biologics.

These enactments governing patent-eligibility for biological patents are specific and limited. In this regard, Congress adopted language in the Leahy-Smith America Invents Act of 2011 (AIA), that prohibits the patenting of "a claim directed to or encompassing a human organism." See Pub. L. No. 112-29, § 33(a), 125 Stat. 284, 340 (2011).

Notably, that bar is expressly limited to patenting "a human organism." It does *not* prohibit patenting *non*-human organisms, such as plants and microbes, much less non-human genes, or even human biological material, such as a gene found in a "human organism."

The distinction—a "human organism" versus all other biological subject matter—is noteworthy. It demonstrates that Congress expressly recognized that biological patents are possible and thereby subject to specific regulation. Congress is well aware that a broad range of biologics is being patented, and in 2007 even considered a bill intended to prohibit the patenting of human genes, but not non-human genes. See H.R. 110-

977. Nonetheless, that bill died in committee. See http://www.govtrack.us/congress/bills/110/hr977. No statute justifies denying isolated human genes—much less isolated *non*-human genes or microorganisms—basic patent-eligibility.

Congress was clear about what should not be patent-eligible—the "human organism." It declined to go further, choosing not to deny patent-eligibility to the very subject matter at issue here—human genes (much less any other biologic). If Congress thought that, before the America Invents Act, § 101 could permit patent-eligibility for the "human organism" itself, thereby necessitating legislation, it would defy logic to conclude that § 101 already denies patent-eligibility to other biologics.

The foregoing underscores that Congress is not only the arm of government best suited to enact policy changes, but also that it takes that responsibility seriously. This Court should refrain from forcing Congress's hand and adopting a position that would disturb the current practice and understanding that biological isolates are, as a general matter, patent-eligible.

As this Court recognized in another patent case, *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, "Congress can legislate [a patent-law principle, such as the patent-eligibility of isolated biologics] out of existence any time it chooses. The various policy arguments now made by both sides are thus best addressed to Congress, not this Court." 535 U.S. 722, 733 (2002) (quoting *Warner-Jenkinson Co.* v. *Hilton Davis Chem. Co.*, 520 U.S. 17, 28 (1997) (quotation marks omitted)). See also, *e.g.*, 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001) (U.S. Patent & Trademark Office's Utility Guidelines, cmts. 2-5) (confirming the patentability of isolated genes).[12]

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[12] CropLife appreciates the serious questions petitioner raises regarding the alleged inaccessibility of Myriad's patented technology

C. The state of the record supports neither reversal nor entertaining issues beyond compliance with § 101

This case comes to the Court on a summary-judgment record. For pure questions of law—such as patent-eligibility of subject matter with undisputed properties—that is perfectly appropriate. But, at this late stage, petitioner seeks to bolster his case by introducing new evidence and engaging in a novel analysis about the reading and scope of these particular claims that is wholly improper. The Court should firmly reject that approach. It should confine its analysis to the legal question of whether isolates of biologics (or even just isolates of human genes), as described above, are patent-*eligible*, and, based on the record below, determine whether petitioner is entitled to the relief he now seeks. Furthermore, whether the claims are, despite their patent-eligibility, deficient for other reasons, is a question best left for a case that properly raises those issues.

1. Petitioner improperly seeks to introduce new evidence to support his § 101 argument that is substantively insufficient

One line of petitioner's § 101 argument is that the BRCA genes at issue here in fact exist in nature as fragments. But, by relying on evidence that is not in the Record, petitioner seeks to make this Court a tribunal of

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to certain patients, under certain circumstances. See, *e.g.*, Pet. Br. 8. To the extent incidents such as these require redress, the response should be properly tailored, directed at responding, in a proportional manner, to the underlying facts and circumstances responsible for them. Under *eBay Inc.* v. *MercExchange, L.L.C.*, 547 U.S. 388 (2006), access to the claimed subject matter can be provided where the equities, particularly the public interest, so dictate. But resorting to § 101—or indeed the patent laws at all—for a solution to what is fundamentally a healthcare issue is far too blunt and overreaching a response.

first look rather than final review. And, as it happens, even if that argument were assumed, *arguendo*, to be true, it still would not make his case.

Petitioner asserts that human DNA fragments can be found in human plasma and blood that "are identical to the fragments created by Myriad when it isolates the gene." Pet. Br. 10-11; see *ibid.* & nn.2-3. This is hardly an assertion unaccompanied by "no genuine dispute as to any material fact," Fed. R. Civ. P. 56(a), as required on a summary-judgment record.

None of the art petitioner cites to support this proposition teaches that any such "floating" DNA fragments actually correspond to a human BRCA gene and are otherwise freed from other cellular components. As described at length above, the "isolated" state of the gene is precisely what the § 101 inquiry must focus upon—and is a limitation present in the claims themselves. See *infra* Part D.1.b (describing why the claims cover only versions of the BRCA genes that are freed from other cellular components).

It would be imprudent, at best, to rely (as petitioner has) on mere conjecture or possibility in concluding that fragmented forms of the human BRCA genes, disassociated from the cellular components that accompany them in the cell, are inherently present in human plasma and blood and, hence, satisfy the "isolated" limitation of the claims-at-issue. Accord *Trintec Indus.* v. *Top-USA Corp.*, 295 F.3d 1292, 1297 (Fed. Cir. 2002); *W.L. Gore & Assocs., Inc.* v. *Garlock, Inc.*, 721 F.2d 1540, 1554 (Fed. Cir. 1983). Indeed, *even if* there are BRCA "fragments" in human blood, any reasonable understanding would be that those fragments would be associated with other cellular components as in every other natural occurrence of the genes. That view is both consistent with science and is contrary to the one that petitioner requires to derive any value from his "fragment" argument.

2. Petitioner raises matters properly addressed under § 112 in the guise of § 101

Relatedly, petitioner also seeks to raise issues regarding the breadth of the claims that are unrelated to whether they effectively cover the BRCA genes as they exist in humans. He contends that the claims-at-issue are tantamount to covering *all* diagnostically-significant versions of human BRCA genes *as they occur in nature*. See, *e.g.*, Pet. Br. 14, 16.[13] This view is both analytically flawed and obscures the real question for the Court—whether those genes *as isolates* are patent-eligible. At best, it raises issues that should be addressed under the finer filter of § 112 of the Patent Act (which measures the claims' written support and enablement) rather than the coarse filter of § 101 (which focuses on patent-eligibility). See, *e.g.*, *Ultamercial, LLC* v. *Hulu, LLC*, 657 F.3d 1323, 1326 (Fed. Cir. 2011); *Regents of the Univ. of Cal.* v. *Eli Lilly & Co.*, 119 F.3d 1559, 1567 (Fed. Cir. 1997). Cf. *Bilski* v. *Kappos*, 130 S. Ct. 3218, 3235-3236 (2010) (Stevens, J., concurring in judgment). The fact that there *are* other mechanisms for properly aggrieved parties to test these issues is itself an important reason why the Court should confine its analysis to the core § 101 question.

Equally significant, Myriad's compliance with § 112 has not been properly preserved for appeal (much less litigated), and it is not before this Court for adjudication. See Pet. App. 60a. Hence, for this additional reason, petitioner's objections to the breadth of the claims should not be heard now.

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[13] Petitioner gives the impression that every claim-at-issue: (a) covers isolated genomic versions of the human BRCA genes; and (b) does not specify a DNA sequence for such isolates. That is incorrect. Claim 2 of the '282 patent, for example, is limited to a cDNA isolate having the coding sequence recited in SEQ ID. NO. 1, a specific sequence disclosed in the patent's specification. See Pet. App. 10a-11a.

3. *Petitioner's argument amounts to offering claim constructions in a manner inconsistent with* Markman

Petitioner's broad view of the claims trivializes expressly-recited claim language and distorts the scope of the claims. Indeed, by ignoring the language of the claims, petitioner ignores claim elements that explicitly limit the claimed DNA molecules to those bearing particular sequences. Moreover, petitioner's approach asks this Court to exercise the claim-construction authority that should be vested in the first instance in a district court under *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370 (1996). Petitioner has not litigated these present theories in the lower courts, least of all in a way that complies with *Markman*'s analytical framework. While no one disputes that the claims cover isolated versions of the BRCA genes limited by the sequences identified in the claims by "SEQ. ID" numbers, this Court should reject efforts—no matter how they are disguised—to arrive at other claim constructions like a court of first review.

4. *The Court's opinion should not address petitioner's expansive questions*

All of these problems demonstrate the limits on deciding cases arising on a scant summary-judgment record. Such a factually under-developed record should dissuade the Court from relying on untested (yet highly contested) factual assertions by petitioner. It also counsels a prudential result—particularly if the Court has any questions about the patent-eligibility of isolated genes. If that is the Court's leaning, then it should exercise restraint and maintain the *status quo* at least until a proper case arises. Indeed, exercising such restraint is all the more appropriate considering that only one petitioner—and one with questionable standing—in reality remains in the case. See Pet. App. 41a; *supra* p. 4 n.2.

D. Recognizing the patent-eligibility of isolated human genes (or other biologics) is wholly consistent with this Court's case law

1. *Chakrabarty's basic requirements are clearly met*

The claims at issue here satisfy *Chakrabarty*'s carefully enunciated test for patent-eligibility. The claimed isolates are made by man and do not exist in nature. That should be sufficient to resolve the § 101 question. The Federal Circuit, while reaching the correct result, deviated from this analysis, and the Court should correct that error in its opinion.

a. As reflected in *Chakrabarty*, Congress intended patent-eligible subject matter to "'include anything under the sun that is made by man.'" See 447 U.S. at 310 (quoting S. Rep. 82-1979, at 5 (1952); H.R. Rep. 82-1979, at 6 (1952)). To ensure that Congress's intention is fulfilled, the Court adopted a bright-line test for determining whether a composition of matter is patent-eligible: is the composition impermissibly directed to "nature's handiwork" or, instead, properly directed to a "human-made invention," *i.e.*, something created by man and, hence, that has a distinctive name, character, or use? See 447 U.S. at 309-310.[14]

At issue in *Chakrabarty* was the patent-eligibility of bacteria that had been genetically engineered with foreign DNA to be capable of digesting crude oil, a trait the bacteria did not naturally possess. 447 U.S. at 305. This Court found such subject matter patent-eligible because the introduction of the foreign DNA into the bacteria was not a natural event but one brought about by man's handiwork. It was human intervention that gave the bacteria a "distinctive name, character [or] use." *Id.* at 309-310.

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[14] This is not to say that every man-made invention always differs *per se* from something that already exists in the prior art, including in nature. See, *e.g.*, the cases cited in nn. 10-11 of the Pet. App. 48a-49a. But it is the province of §§ 102 and 103 of the Patent Act, not § 101, to prevent the issuance of claims that, *although directed to patent-eligible subject matter*, lack novelty or non-obviousness. This case addresses only § 101, and a holding that Myriad's claims satisfy § 101 takes no position as to whether they satisfy any other provision of the Patent Act.

b. Although the Federal Circuit reached the correct outcome in this case, it strayed from *Chakrabarty*'s test. It introduced imprecision into the analysis by holding that the isolated versions of the BRCA genes were patent-eligible because they are "markedly different from" their naturally-occurring counterparts present in the body. See Pet. App. 40a, 45a, 50a, 52a.

Under *Chakrabarty*, that approach is unnecessary. Compared to the composition found patent-eligible in *Chakrabarty*, the compositions claimed here are equally distinctive and equally reflect the handiwork of man, not nature. This is evident from the claims' focus on *isolated* DNA molecules. For decades, the term "isolated" (like the term "purified") has been used in patent claims to distinguish isolates from genes as they occur in nature, which are associated with other cellular components such as proteins and other DNA molecules. See Pet. App. 18a-20a. The term "isolated" therefore reflects that, with the aid of human intervention, the claimed DNA molecules are molecules that: (a) are not part of human chromosomes, and, hence, not chemically linked to DNA sequences that naturally flank such molecules in their natural chromosomal environment in human cells; and (b) are freed from other components that co-exist with human genes in a cell.

The patent employs the term "isolated" in a consistent fashion.[15] Hence, the requirement that the claimed DNA molecules take the form of "isolates" emphasizes their man-made quality and distinguishes them from the human BRCA genes found in nature. That crucial feature, and its distinctiveness, is all that is required under *Chakrabarty* to satisfy § 101.

To the extent the Government and other *amici* urge that patent-eligibility should turn on whether the isolated gene is in a genomic or cDNA form, that analysis is unsound and should be rejected. See U.S. Br. 18-20; Lander *Amicus* Br. 26-29. First, the distinction generally only has meaning with respect to genes found in higher organisms such as humans; lower organisms, such as those of interest to CropLife's members, typically lack introns. Hence, genomic and cDNA versions of the latter genes are essentially indistinguishable from each other in terms of their sequences. Second, the analysis is inconsistent with *Chakrabarty*, which allows *any* distinctiveness—attributable to man's handiwork—to provide a basis for patent-eligibility. Again, an isolated biologic, whether a genomic version or cDNA version of a gene or something else, meets that test: with the benefit of human intervention, the biologic is freed from the materials that its natural counterpart is associated with.

2. *No precedent cited by petitioner impairs the patent-eligibility of isolated human genes or other biological isolates*

Contrary to the foregoing analysis of *Chakrabarty*'s core requirements, petitioner argues that claims covering isolated versions of a human gene do not pass muster under *Chakrabarty* and other precedents of this Court as patent-eligible compositions of matter. He asserts that such subject matter fails to satisfy any of the three alternative "tests" purportedly created by these precedents and against which a composition's patent-eligibility should purportedly be judged, namely: (a) does the claimed subject matter have markedly different characteristics from what is found in nature?; (b) is the claimed subject matter based on an inventive concept?; and (c) does the claimed subject matter preempt what nature has provided? See Pet. Br. § I.

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[15] The '282 patent, col. 19, ll. 8-18, defines "an isolated nucleic acid" as one "substantially separated from other cellular components which naturally accompany a native human [nucleic acid] sequence, *e.g.*, ribosomes, polymerases and many other human genome [nucleic acid] sequences and proteins. The term embraces a nucleic acid sequence * * * which has been removed from its naturally-occurring environment, and includes recombinant or cloned DNA isolates." J.A. 755.

But this Court has never held ineligible for patent protection a biologically-based composition of matter. Quite to the contrary, it has recognized the eligibility of such subject matter, finding the bacterial cultures claimed in *Funk* and *Chakrabarty* to be man-made compositions that are different from what occurs in nature. Petitioner has misconstrued these and other precedents and, in turn, has improperly applied them (and the foregoing "tests") to the subject matter now at issue. In fact, many of these decisions focus on entirely different issues and concerns than the question presented here: inventiveness/non-obviousness (*Funk*); what qualifies as an "article of manufacture" (*American Fruit*); and avoiding the preemption of a law of nature (*Mayo*).

a. Funk *solely concerns whether claims lacked "invention," i.e., were "obvious," not whether they are patent-eligible*

The issue in *Funk* was not patent-eligibility but "lack of invention" (or what one might call "lack of inventiveness"). Such a deficiency is synonymous with our modern concept of "obviousness" under 35 U.S.C. § 103.

The claims in *Funk* were directed to combinations of various strains of bacteria that can be used as "inoculants" to assist any leguminous plant in absorbing nitrogen. *Funk Bros.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 128-129 (1948).[16] The Court readily credited the patentee with making "a new and different composition" compared to what is provided by nature. *Id.* at 130. That is the § 101 inquiry. The Court found, however, that it "fell short of invention"—that is, that what was made was insufficiently inventive.[17] 333 U.S. at 131; see *id.* at 128, 132. *That* examination is wholly unrelated to § 101, which underscores that subject matter, like that in *Funk*, may simultaneously be patent-eligible yet invalid for "obviousness."

Hence, patent-eligibility was not the issue in *Funk*; obviousness was.[18] See also Pet. App. 49a (noting this point). Indeed, the claimed mixtures of bacteria were clearly compositions created by man. Although the individual strains present in those compositions exist in nature, it was man, not nature, who uniquely took them and combined them together.

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[16] Prior art had taught that individual strains of bacteria could selectively work with a particular species of a leguminous plant and, further, that combining distinct species of bacteria to treat fields containing mixed leguminous crops generally did not work since the various strains tended to inhibit each other's nitrogen-fixing capabilities. *Funk*, 333 U.S. at 129-130. Hence, the patentee's invention was premised on the surprising discovery that certain species of bacteria could be successfully combined to treat any leguminous crop without producing an inhibitory effect on nitrogen-fixation. See *ibid.*

[17] To the Court, the discovery that certain bacterial strains were not mutually inhibitory of one another was nothing more than discovering nature's handiwork, *i.e.*, that nature had conferred compatibility among these bacterial strains for nitrogen-fixing. Relying on that "natural phenomenon" to combine such bacterial strains into prepackaged compositions convenient for sale and application to crops was not considered to be inventive activity on the part of the patentee. 333 U.S. at 131. Because condoning the *validity* of claims to such subject matter was viewed as effectively granting a patent on an *obvious application* of one of nature's heretofore unknown secrets, the Court invalidated the claims. *Id.* at 132.

[18] That the concept of "invention," as *Funk* called it, is synonymous with the modern concept of "non-obviousness," is underscored in the current Patent Act's legislative history. It makes clear that the re-

If *Funk* has any relevance here, it does not aid petitioner. *Funk* simply illustrates that the Patent Act has sufficiently powerful filters to remove claims even if they satisfy § 101's threshold—even those directed to compositions that in some fashion can be said to be based on or derived from what is otherwise found in nature.[19]

b. Petitioner relies on dicta *in* Chakrabarty *distinguishing man's handiwork from nature's—but isolated versions of a human gene respect that distinction*

As petitioner correctly observes, *Chakrabarty* cites *Funk* and notes that the genetically-engineered bacteria Chakrabarty created had "markedly different characteristics from the bacteria found in nature." 447 U.S. 310.

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quirement was a judicially created doctrine, which Congress was codifying for the first time as § 103. See S. Rep. 82-1979, at 4, 6; H.R. Rep. 82-1979, at 5, 7.

[19] Since the jurisprudence on obviousness has evolved since *Funk*, it is unlikely that the same result would be reached today. First, with the enactment of § 103, the concept of "inventiveness/non-obviousness" has been expanded such that patentability "should not be negatived by the manner in which the invention was made"—*e.g.*, drawing on a law of nature, as the patentees in *Funk* had. See 35 U.S.C. § 103(a). Second, subject matter is considered non-obvious under § 103 if it produces a result that could not have been predicted. See *KSR Int'l* v. *Teleflex, Inc.*, 550 U.S. 398, 416-417 (2007). Measured against this yardstick, the patentee in *Funk* went against the grain of conventional wisdom and surprisingly demonstrated that select strains of the bacteria could in fact be combined in a compatible fashion. Compare, *e.g.*, *In re Brimonidine Pat. Litig.*, 643 F.3d 1366, 1376 (Fed. Cir. 2011) (finding the compatibility between two ingredients in an eye-drop formulation to be non-obvious).

But this discussion is descriptive *dicta*, not a new test. It draws on the facts of *Funk*, an obviousness case, as a foil to dramatically illustrate that Chakrabarty's invention reflected man's handiwork, not nature's: genetically-engineering bacteria to possess the novel trait of being able to decompose crude oil necessarily reflected the hand of man, because Chakrabarty's bacteria were unlike any occurring in nature.[20]

Finding isolated versions of a human gene, such as the BRCA genes, patent-eligible respects the "man versus nature" distinction. *Patent-eligibility* for such subject matter *is not* predicated on discovering a heretofore hidden secret of nature, such as these genes' existence, their specific DNA sequences, or their ability to predict a predisposition to cancer. Rather, it is predicated on the fact that isolated versions of these genes, by virtue of man's intervention, are different molecules—different compositions of matter—than what exists in the body.

c. American Fruit *addresses "articles of manufacture," not "compositions of matter"*

The issue before the Court in *American Fruit Growers, Inc.* v. *Brogdex Co.* was whether the claimed subject matter (a citrus fruit, the rind of which was impregnated with borax to be resistant to fungal decay) qualified as an "article of manufacture," which was one of the statutory classes eligible for patent protection under former 35 U.S.C. § 31. See 283 U.S. 1, 11 (1931). The present case, of course, involves patent-eligibility for "compositions of matter," an entirely different statutory class of invention.

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[20] Although the patentee in *Funk* could not take credit for the claimed bacteria working in a cooperative fashion when it comes to nitrogen-fixing, the acts of assembling the bacterial strains into "all purpose" compositions reflects human handiwork and is, hence, sufficient for claims directed to the same to be patent-eligible. See *supra* Part D.2.a. Nothing in *Chakrabarty* detracts from that logic and disqualifies such acts as being sufficient to cross § 101's threshold.

The *American Fruit Growers* Court resolved the issue before it by consulting Century Dictionary's definition of "manufacture," and, based on that definition, concluded that articles of manufacture, per § 31, required producing materials with "'new forms, qualities, properties, or combinations.'" 283 U.S. at 11. Adding borax to a fruit rind was deemed not to "change the name, appearance, or general character of the" underlying fruit; the claims were thus held not to be directed to an article of manufacture within § 31's meaning.

The Court's analysis was performed solely to inform the inquiry of whether the former could be characterized as an "article of manufacture." That inquiry has nothing to do with this case, and recognizing isolated human genes as patent-eligible does not offend *American Fruit Growers* in the least. That is because isolated genes, being molecules, *i.e.*, "arrangements of atoms," squarely qualify under § 101 as "compositions of matter," a statutory class that is distinct from "articles of manufacture." See, *e.g.*, D.S. Chisum, Chisum On Patents § 1.02[2], p. 1-14 (2012). There is no need to test whether isolated human genes qualify as "articles of manufacture" under *American Fruit*.

Even, assuming *arguendo*, that the presence of a "marked difference" were a proper way to identify patent-eligible subject matter, isolated versions of the human BRCA genes would satisfy that test. Whereas genes as they exist in the human body serve only the function of encoding mRNA and/or proteins, the claimed isolated genes can be put to use for the very important, and life-saving purpose, of diagnosing breast and ovarian cancer. Genes, as they exist in nature, cannot serve this purpose. See Pet. App. 51a-52a, 82a; Resp. Br. 35. Even petitioner concedes this point. Pet. Br. 34 n.9.[21]

d. Mayo *concerns the patent-eligibility of processes, but isolated versions of a human gene qualify as compositions of matter*

As previously noted, *Mayo* considered whether certain claimed processes were impermissibly directed to a natural law or properly directed to patent-eligible applications of those laws. 132 S. Ct. at 1294. This Court noted that, to be patent-eligible, a claim may only recite a law of nature if it recites "additional features that provide practical assurances that the [claimed] process is more than a drafting exercise designed to monopolize the law of nature itself." *Id.* at 1297. See also *Diamond* v. *Diehr*, 450 U.S. 175 (1981).

In contrast to the claims at issue in *Mayo*, the claims here are directed to DNA molecules, which, again, are compositions of matter. Cf. *supra* Part D.2.c. These claims do *not* recite a "natural law." Thus, there is no need to inquire into whether the claims recite language that ensures that they are directed to a patent-eligible application of a natural law, as opposed to just the law itself. See Pet. App. 44a.

To be sure, claims to a composition of matter can raise concerns parallel to these articulated in *Mayo*, *i.e.*, that product claims may impermissibly preempt natural phenomena. But by virtue of being directed to "isolates,"

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[21] Petitioner tries to negate such utility by noting that an isolate must be labeled, *e.g.*, via "fluorescence," in order to function as a probe. While that may be true, it is a distinction without significance. Such a probe still contains and employs the DNA isolate as a component and, hence, falls within the scope of the claims at issue. Moreover, even if petitioner were to argue that the sequence of the DNA isolate needs to be modified so that the label can be incorporated, that distinction similarly lacks any significance since petitioner has argued that the claims are broad enough to read on isolates with derivitized sequences. See Pet. Br. 13-14.

Myriad's claims exclude human genes as they naturally occur in the human body from their scope. In this respect, the claim limitation "isolated" serves an analogous function as claim elements do in a process claim that ensure that the subject matter being claimed is an application of the law of nature, and not the law itself; it ensures that human genes as they occur in nature are not being preempted. Critically, humans carrying the BRCA genes do not infringe such claims because they are not making, using, or selling *isolated* versions of such genes.[22] See Section D.1.b., *supra*.

Finally, other considerations further caution why *Mayo* should not be extended, as petitioner urges, to resolving whether a composition of matter claim is impermissibly directed to a natural phenomenon. Principally, such an extension would lead to an absurd result that conflicts with *Chakrabarty*. This can be readily appreciated considering the application of petitioner's position to claims directed to genetically-modified seeds and plants—subject matter of keen interest to CropLife's members.[23] If the gene isolate were deemed *per se* patent-ineligible as a natural phenomenon, one would only be left to point to generic language that refers to the seed or plant that bears the gene as conferring patent-eligibility to the claim. The generic concept of creating a seed or plant transformed by a gene could be viewed as implicating "conventional" activity, which, per *Mayo*, is insufficient to take the claim across § 101's threshold.

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[22] Petitioner repeatedly highlights that the claims cover any use of the isolated human BRCA genes, insinuating that the claims have an unjustified reach. See, *e.g.*, Pet. Br. 11. What petitioner fails to appreciate, however, is that *any composition claim* entitles the patentholder to enforce it against *any use* of the subject matter it covers. See, *e.g.*, 35 U.S.C. § 271(a). Accord Pet. App. 58a-59a. Hence, the exclusionary power to which the claims-at-issue are entitled is no different than that conferred under any composition patent.

[23] A sample claim would be: "A seed/plant comprising a DNA molecule having the nucleic acid sequence of SEQ. ID No. X."

And yet *Chakrabarty* clearly instructs that this threshold is successfully crossed when a substrate (a bacterium) is transformed with DNA (a plasmid) so as to impart a novel trait to it (oil digestion). As between extending *Mayo's* holding versus preserving the holding in *Chakrabarty*, the latter is the sounder course—especially since petitioner takes no issue with the manner in which *Chakrabarty* was resolved.

CONCLUSION

This Court's precedents regarding patent-eligibility under 35 U.S.C. § 101 have served the country well in advancing science and the useful arts and, if reaffirmed, will continue to do so. This Court should therefore maintain its broad interpretation of § 101 and affirm the Federal Circuit's judgment that the claims at issue in this case are patent-eligible under § 101. Isolated versions of human genes sufficiently reflect man's handiwork—per *Chakrabarty*'s interpretation of what subject matter Congress intended to be patent-eligible—that claims so directed merit the same protections afforded by the law to other new and useful inventions.

Respectfully submitted.

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AMICUS CURIAE BRIEF

RECORD
AND
BRIEFS

Supreme Court, U.S.
FILED
JAN 31 2013
OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

◆

ASSOCIATION FOR MOLECULAR
PATHOLOGY, *et al.*,
Petitioners,
—v.—
MYRIAD GENETICS, INC., *et al.*,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF FOR *AMICI CURIAE* OF THE ETHICS & RELIGIOUS LIBERTY COMMISSION OF THE SOUTHERN BAPTIST CONVENTION AND PROF. D. BRIAN SCARNECCHIA IN SUPPORT OF PETITIONERS

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INTEREST OF THE *AMICI CURIAE*[1]

The patents at issue in this lawsuit were granted on two genes related to breast cancer and ovarian cancer and on using those genes to determine if a person has a predisposition to cancer. These patents, exclusively licensed to Myriad Genetics, Inc., violate the religious principle of *Amici Curiae* that the human body and its parts should not be owned, a belief akin to the legal principle that products of nature, laws of nature and natural phenomena are not subject matter eligible for patent protection. Significantly, because the gene patents at issue cover everyone's BRCA1 and BRCA2 genes, the patents put the *Amici Curiae* in the untenable position of being personally subject to patents that violate their religious beliefs.

Amicus Curiae the Southern Baptist Convention is America's largest non-Catholic denomination with more than 16.2 million members in over 44,000 churches nationwide. Southern Baptists hold the belief that the genetic code should not be owned. Southern Baptist Convention,

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[1] No counsel of a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief and no person other than amici curiae, its members, or its counsel made a monetary contribution to its preparation or submission.

Petitioners have provided written consent, on file with the clerk, to the filing of briefs in support of either, or neither, party, and respondents provided consent, on file with the clerk, for the filing of this brief on Jan. 31, 2013.

Resolution on the Patenting of Animal and Human Genes (June 1995), *available at* http:// www.sbc.net/ resolutions/amResolution.asp?ID=570.

Amicus Curiae Prof. D. Brian Scarnecchia, M.Div., J.D. is an Associate Professor of Law at Ave Maria School of Law in Naples, Florida where he has taught Property Law and Bioethics. He is also the Director of the Human Life Studies program at Franciscan University of Steubenville in Steubenville, Ohio. He is the author of BIOETHICS, LAW AND HUMAN LIFE ISSUES: A CATHOLIC PERSPECTIVE ON MARRIAGE, FAMILY, CONTRACEPTION, ABORTION, REPRODUCTIVE TECHNOLOGY, AND DEATH AND DYING (2010). He is also the founding president of International Solidarity and Human Rights Institute (ISHRI), a non-governmental organization (NGO) in consultative status with the United Nations. Scarnecchia believes that the patenting of DNA sequences treats as private property what is a part of the common and innate nature of the human person. Patents on DNA sequences will open the door to further commodification of the gene pool reflecting a eugenic mentality as, for instance, in germ line cell therapy. For these reasons, individually and as a president of ISHRI, he presents this brief to the Court.

SUMMARY OF THE ARGUMENT

Products of nature, which are gifts given to all of humanity by God, cannot be exclusively claimed by an individual or corporation. The genetic code is a divine gift and an intrinsic, inseparable part of human existence. Permitting a corporation or person to own this fundamental component of a person corrupts the relationships between human beings and the Creator, and between human beings. The person should not be treated as a commodity for sale to the highest bidder, and property must be recognized in a way that respects all of the members of society. These principles are prevalent in Christian theology, and several religious organizations specifically oppose gene patents on these grounds.

These moral principles regarding patents are reflected both in American law and the international community. Patent law emphasizes that the human body is not subject to ownership. Likewise, America's rich legal tradition has provided strong protections against the control of the person by others. The international community echoes these ideals in their opposition to human gene patents. Permitting human DNA patents violates the spirit of patent and property law by permitting a single entity to claim a product of nature, thereby asserting control over the human genetic patrimony. This results in harms to all people, especially vulnerable people who are in the greatest need of options and access in medicine.

ARGUMENT

Myriad Genetics' patents claim the BRCA1 and BRCA2 breast cancer gene sequences. These sequences are isolated nucleic acids. Isolated nucleic acids (e.g., RNA, DNA, or a mixed polymer) are acids that are separated from other cellular components that naturally accompany a native human sequence or protein. Because all that it has done is remove the DNA from the body, Myriad Genetics' assignor has patented the DNA.

Myriad Genetics argues that this Court should grant exclusive ownership rights over genetic material that is essential to human existence. It seeks to commodify this information, disregarding its intrinsic value and nature as a divine gift. In doing so, Myriad Genetics ignores the values that are interwoven into the laws and morals of American society.

This case presents this Court with an opportunity to preserve the constitutional foundation of the U.S. patent system, while extinguishing serious threats to the values on which our nation was built.

I. The Genetic Code is a Necessary Part of Human Existence, Created by God.

DNA is necessary for human existence. Christian churches hold as a core principle that God created DNA. Granting ownership of DNA upsets the fundamental relationship between human beings and God, both because it commodifies the human body—degrading its dignity within creation—and consigns an essential part of the human genetic patrimony to private ownership. Numerous churches have expressed concern over the patenting of genetic material for these reasons.

A. The genetic code is necessary for human existence.

DNA is not simply a chemical sequence that can be manipulated and owned by scientists—it is essential to human existence. DNA holds a dignified place in creation—it is not a human invention, but a divine one. It is the "biological blueprint for human beings as images of God." Mark J. Hanson, *Religious Voices in Biotechnology: The Case of Gene Patenting*, HASTINGS CENTER REP. 1, 4 (1997). Similar to a "new plant found in the wild," the gene sequences claimed by Myriad Genetics occur naturally in the human body. *Diamond v. Chakrabarty*, 100 S. Ct. 2204, 2209 (1980) (emphasis added) (quoting and contrasting *Funk Bros. Seed Co.*, 68 S. Ct. 440, 441 (1948)). DNA, a gift written into nature itself, is not appropriate material for private patents. See John Paul II, *Message of the Holy Father for Lent 2002*, Oct. 4, 2001, *available at* http://www.vatican.va/holy_father/john_paul_ii/messages/lent/documents/hf_jp-ii_mes_20020205_lent-2002_en.html at para. 2 [hereinafter *Lenten Message*] ("[B]ecause it is gift, life can never be regarded as a possession or as private property, even if the capabilities we now have to improve the quality of life can lead us to think that man is the 'master' of life."). The genetic code is at the heart of humanity's existence and cannot be owned, any more than the "immortal soul of Christianity" can be controlled by humans. DOROTHY NELKIN & M. SUSAN LINDEE, THE DNA MYSTIQUE: THE GENE AS A CULTURAL ICON 40 (2004). President Bill Clinton spoke to the exalted nature of the gift of DNA when he announced the completion of the Human Genome Project in 2000: "Today we are learning the language in which God created life." President Bill Clinton, Remarks on the Completion of the First Survey of the Entire Human Genome Project (June 26, 2000), *available at* http://www.ornl.gov/sci/techresources/Human_Genome/project/clinton2.shtml.

B. Ownership of DNA upsets the fundamental relationships between God and humanity, and between human beings.

Allowing anyone to claim ownership over the very material that constitutes the human body reverses the roles of the Creator and the created. Like any effort to claim ownership over the person, it results in "an audacious usurpation of the Divine prerogative, a daring infringement of the law of nature, and a base over-throw of the very foundations of the social compact." William Lloyd Garrison, *Declaration of Sentiments of the American Anti-Slavery Convention*, Dec. 6, 1833, *available at* http://utc.iath.virginia.edu/abolitn/abeswlgct.html. Specifically, granting private exclusive rights over a part of the human body—especially one as central to human existence as DNA—degrades humanity, dropping it from its special role in creation to a mere species of property. Second, as an essential part of God's creation, human DNA should be held in common by all humanity so that it can be put to the service of all of its members.

Humanity's genetic material grants individuality, even as it ties all people together. "All men have the stars, but they are not the same things for different people." ANTOINE DE SAINT-EXUPÉRY, THE LITTLE PRINCE 85 (Katherine Woods trans., 1943). This combination of common patrimony with individual effects is a fundamental aspect of genes echoed by religious leaders, and it confers moral responsibilities: "The originality of every person is a consequence of the particular relationship that exists between God and a human being from the first moment of his existence and carries with it the obligation to respect the singularity and integrity of each person, even on the biological and genetic levels." Congregation for the Doctrine of the Faith, *Instruction* Dignitas Personae *on Certain Bioethical Questions*, Sept. 8, 2008, *available at* http://www.vatican.va/roman_curia/congregations/cfaith/documents/rc_con_cfaith_doc_20081208_dignitas-personae_en.html.

The gene, as a chemical compound, operates according to the natural laws of the genetic code. *See* Eileen M. Kane, *Splitting the Gene: DNA Patents and the Genetic Code*, 71 TENN. L. REV. 707, 710 (2004). The genetic code, operating in accordance with the natural laws set forth by the Creator, is a product of the divine mind. This Court has made clear that although natural substances can be extracted from their source, "the extract is the same, no matter from what it has been taken." *Am. Wood-Paper Co. v. Fibre Disintegrating Co.*, 90 U.S. (23 Wall.) 566, 594 (1874). The genetic code is a component of divine creation, both within and outside the body.

Attempting to divvy up the person to the highest bidder for commercial purposes runs the "serious risk of suppressing the person's very nature" and reducing him to a mere object. *See* John Paul II, Address to the Pontifical Academy of Sciences (Oct. 28, 1994), *available at* http://www.its.caltech.edu/~nmcenter/sci-cp/sci94111.html [hereafter "Pontifical Address"]; Samuel J. Kerstein, *Kantian Condemnation of Commerce in Organs*, *available at* http://www.philosophy.umd.edu/Faculty/SKerstein/Kantiancondemnation.pdf (allowing people to commodify parts of themselves degrades them to the level of mere objects, robbing them of freedom, dignity, and self-respect).

C. These Principles Run Throughout Christian Theology.

Many major religious denominations have vehemently opposed patents over genetic material, including the Southern Baptist Convention, the Catholic Church, the United Methodist Church, and the World Council of Churches. Their viewpoints address the risk genetic patents pose to the sacred relationship between humans and their Creator posed by genetic patents.

1. The Southern Baptist Convention

The Southern Baptist Convention believes that every human being is made in God's image and possesses unique value derived from humanity's intimate relationship with him. "So God created man in His own image, in the image of God He created him . . . ." *Genesis* 1:27 (New Living Translation). Human dignity flows from this relationship, and "[h]uman DNA symbolizes something essential about humans themselves, and, as such, raises the issue of human dignity." Miriam Schulman, *Of SNPS, TRIPS, Human Dignity: Ethics and Gene Patenting*, 1 BIOPROCESS INT'L J. 26 (2003). The patenting of human genetic material is an attempt to seize the power of, and ownership over, creation from God. "God wrote those sequences of C, G, A & T. It is heresy, or at least plagiarism, for [anyone else] to claim to do so." James Boyle, *Enclosing the Genome: What the Squabbles Over Genetic Patents Could Teach Us*, 50 ADVANCES IN GENETICS 97 (2003), *available at* http://web.law.duke.edu/ip/pdf/enclosing.pdf. This principle is seen throughout the Judeo-Christian tradition that forms the basis for the moral principles of our legal tradition.

2. The Catholic Church

The Catholic Church is devoted to the protection of human dignity and the "incomparable worth of every human person." *See, e.g.*, John Paul II, *Evangelium Vitae*, Mar. 25, 1995, para. 2, *available at* http://www.newadvent.org/library/docs_jp02ev.htm. "With the new prospects opened up by scientific and technological progress," Pope John Paul II noted, "there arise new forms of attacks on the dignity of the human being. *Id.* at para. 4. "Respect for life requires that science and technology should always be at the service of man and his integral development," respecting human dignity as a primary obligation. *Id.* at para. 81.

Gene patenting does not show this respect. It asserts exclusive rights over "[God's] gift, his image and imprint, [the] sharing in the breath of life." *See id.* at para. 39. In an address to the Pontifical Academy of Science, Pope John Paul II emphasized that dignity and DNA are bound to each other: "Man cannot be separated from his DNA any more than he can be separated from his spirit." *Pontifical Address, supra.* He then charged the Academy, and all genetic researchers, not to lose sight of this core of human existence in the pursuit of scientific progress—urging them to "take into consideration the metaphysical and moral questions that become even more pressing when the certitude obtained by science is seen in relation to the whole truth about man." *Id.* Myriad Genetics has not done so, attempting to isolate genetic information and contradicting the truth that the human person is not mere chattel to be parceled out.

3. The United Methodist Church

The United Methodist Church has also expressed concerns about human gene patenting, proclaiming that the ownership of genetic information is a violation of "the sanctity of God's creation and God's ownership of life". Steven Goldberg, *Gene Patents and the Death of Dualism*, 5 S. CAL. INTERDISC. L.J., 25, 34 (1996). The church believes that "humans and animals are creations of God, not humans, and as such should not be patented as human inventions."

Ronald Cole-Turner, *Religion and Gene Patenting*, 270 SCI. 52 (1995). This position gained world-wide attention and was featured on the front page of the *New York Times*. Goldberg at 34.

In 1988, the church formed a committee to address the religious and moral implications of gene patenting. The committee drafted ethical recommendations against gene patenting that were eventually adopted in the 1996 Joint Appeal—a statement released by 200 religious leaders from various religions addressing gene patents. United Methodist Church, *BRCA Statement of Support: United Methodist Board of Church and Society*, May 12, 2009, *available at* http://www.aclu.org/free-speech/brca-statement-support-united-methodistboard-church-and-society. These leaders called for an end to the patenting of genetic material and expressed grave concerns about recent decisions on the part of the Patent Office.

4. The World Council of Churches

The World Council of Churches (WCC) brought the danger of genetic patents to the attention of religious communities in 1989 when it published *Biotechnology: Its Challenges to the Church and World*. It has remained a leader in this important struggle. At a 1999 United Nations meeting, the WCC joined over 80 signatories representing indigenous peoples in opposing the patenting of human genetic material. "The World Council of Churches is opposed to the buying. and selling of human body parts. This includes the patenting of human genes. The dignity of the human person is irreconcilable with any commodification of human life. Human life is commodified when its value is weighed against another value. This is what happens when human life is patented. Such patenting gives power over human life to specific human beings that cannot be justified. Life ultimately belongs to God. The patenting of human life is in opposition to this conviction." World Council of Churches, Justice, Peace and Creation Team, *Genetic, Agriculture and Human Life*, approved by the WCC Executive Committee General Assembly Feb. 2006.

This statement was issued on behalf of over 560 million Christians in member churches worldwide and shows a clear concern for the potential degradation of human dignity. *See* World Council of Churches, *Who We Are*, http://www.oikoumene.org/en/who-are-we.html. Myriad Genetics' gene patents, by commodifying human life, are an affront to these universally recognized principles of human dignity.

II. These Theological and Moral Principles are Reflected in American Law and the International Community.

Private property rights over natural resources are recognized for their ability to promote human flourishing. They do not exist to promote selfish gain. Rather, they protect and serve humanity. Accordingly, both American law and the international community affirm that there should be limits on private property rights over elements of creation, including the human body.

A. Patent law

Patent law considers utility to be of the highest importance in deciding whether to grant property rights. "A [patent] application must show that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research." *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005) (holding that to satisfy the "substantial" utility requirement, an asserted use must show that that claimed invention has a significant and presently available benefit to the public). Process and product claims must lead to a result that can be used for some substantial and specific practical end. Michael Risch, *Everything is Patentable*, 75 TENN. L. REV. 591, 607 (2008).

More than a century of legal precedent has established that products and laws of nature are not patentable subject matter, because granting exclusive rights over them would limit further development by others. *See, e.g. Chakrabarty, supra*, at 309 ("Laws of nature, physical phenomena, and abstract ideas are manifestations of nature, free to all men and reserved exclusively to none."); *Funk Bros.* at 130; *Am. Wood-Paper Co.* at 594. The exceptions to 35 U.S.C. § 101 safeguard the constitutional command that patents be granted to inventors only for the purpose of promoting scientific progress—thereby setting a high standard for patent claims involving products of nature. *See* U.S. CONST., art. I, § 8, cl. 8.

B. Property in the person

The genetic code has been recognized as the "most intimate commons of all," gifted to humanity as a whole by the Creator. JEREMY RIFKIN, THE BIOTECH CENTURY 41 (1998). No DNA sequence should be the property of one individual or organization. Daniel Kevles, *Vital Essences and Human Wholeness: The Social Readings of Biological Information*, 65 S. CAL. L. REV. 255, 277. "Scientific work aimed at securing a quality of life more in keeping with human dignity is admirable, but it must never be forgotten that human life is a gift"—one that has been entrusted to all of humanity and must be "received without pay and to be placed without pay at the service of others." *Lenten Message, supra,* at para. 2. Genetic material, essential to the human person, cannot justly be consigned as property to another.

1. The rejection of human beings as property in law

The privatization of humanity is not a new concern for the American legal system. As this country struggled to eradicate slavery, abolitionists argued that the commodification of human beings was an intolerable evil that not only degraded those being bought and sold, but all of society. A person, Frederick Douglass argued, has a "self-evident" right to be free of ownership by others. Frederick Douglass, The Horrors of Slavery and England's Duty to Free the Bondsman: An Address Delivered in Taunton, England (Sept. 1, 1846), *available at* http://www.yale.edu/glc/archive/1081.htm. Douglass asserted that God gave him "these hands, this head, these shoulders," and that to claim possession over even one aspect of another person's body "strikes down all right in striking down one right." *Id.* Denying someone ownership over an aspect of the person, the abolitionists saw, does not deprive him of his property—it restores the gift of life to the one entrusted with it by God. *See* Garrison, *supra*, at 69. ("Freeing the slave is not depriving [the slaveholder] of property, but restoring it to its rightful owner."). The Thirteenth Amendment to the U.S. Constitution, following the abolitionists in rejecting ownership over the person, banned "slavery and involuntary servitude," thus rendering unconstitutional the commodification of human beings. U.S. CONST., amend. XIII.

More recently, Justice Stanley Mosk of the California Supreme Court addressed concern over ownership of the human body in his dissent in the landmark 1990 case, *Moore v. Regents of the Univ. of Cal.*, 793 P.2d 479, 515-16 (Cal. 1990). Treating human material as property, he wrote,

> tends to treat the human body as a commodity—a means to a profitable end. The dignity and sanctity with which we regard the human whole, body as well as mind and soul, are absent when we allow researchers to further their own interests without the patient's participation by using a patient's cells as the basis for a marketable product.

Id. at 516 (citing Mary Taylor Danforth, *Cells, Sales, And Royalties: The Patent's Right To A*

Portion Of The Profits, 6 YALE L. & POL'Y REV. 179 (1988)).

Justice Mosk recognized that the law respects the human body as a unique expression of the self and thus prohibits exploitation of that body. Exploiting the human body in order to further scientific process brings to mind prohibited exploitations of the body, including slavery, cruel and unusual punishments, and indentured servitude. *Id.* at 515.

2. The rejection of human beings as property in religion.

The Southern Baptist Convention agrees with Justice Mosk that allowing ownership of human genetic material is akin to condoning exploitation. "Marketing human life is a form of genetic slavery. Instead of whole persons being marched in shackles to the market block, human gene sequences are labeled, patented, and sold to the highest bidders . . . That the U.S. Patent Office would grant such applications is absolutely chilling." Ethics & Religious Liberty Commission, Southern Baptist Convention, *BRCA – Statement of Support from the Ethics & Religious Liberty Commission*, May 12, 2009, *available at* http://www.aclu.org/free-speech/brca-statement-support-ethics-religious-liberty-commission-southern-baptist-convention; *see also* Richard D. Land & C. Ben Mitchell, *Patenting Life: No*, 63 FIRST THINGS 16 (1996).

The Roman Catholic Church, along with many in the Christian, Jewish, and Islamic traditions, emphasize the fact humans exist in interdependency and have a responsibility for their neighbor's well-being. Although scientific progress is to be encouraged, it becomes an injustice when its fruits are "distributed in such a way that unjust inequalities are actually increased or even rendered permanent." John Paul II, *Jubilee 2000 Debt Campaign*, Sept. 23, 1999, *available at* http://www.vatican.va/holy_father/john_paul_ii/messages/pont_messages/1999/documents/hf_jp-ii_mes_19990923_jubilee-2000-debt-campaign_en.html. Intervening in human genetics is not an inherent problem, for all human beings are called to participate in the creative work of God. However, to give anyone control over another person's body results in the "unjust domination of man" and corrupts the relationships between human beings. *Dignitas Personae* at para. 27.

Human gene patenting has grim implications because it turns the person into a form of property. Granting ownership of humanity's most fundamental genetic matter opens the door for companies to demand more—putting the rest of the human body at risk of commodification as well. This Court has a responsibility to protect individual freedom by refusing to let human genetic material be commodified and sold. Myriad Genetics threatens the sanctity of the genome and the integrity of the person by seeking a patent.

C. The international community

The United Nations has also expressed concern over gene patents, recognizing that "the human genome is the property of 'Humanity'" and a part of our "common heritage." Brian Gargano, *The*

Quagmire of DNA Patents: Are DNA Sequences More Than Chemical Compositions of Matter?, 2005 SYRACUSE SCI. & TECH. L. REP. 3, 5 (Spring 2005). Since this declaration, the idea of common responsibility for the human genome has been adopted across Europe and affirmed by both the U.S. National Research Council and the American Society of Human Genetics. *Id.* British Prime Minister Tony Blair and U.S. President Bill Clinton issued a joint statement declaring the human genome to be a gift from God that is common to all humanity, and as such not something that can be bought and traded among scientists. *Id.* The Roman Catholic Church has condoned the actions of the European directive, finding that the bans against modifying the foundational identity genetic identity of human beings helps to fill in a "legislative gap." Jean-Louis Tauran, *The Defense of Life in the Context of International Policies and Norms*, Feb. 11, 2000, *available at* http://www.vatican.va/roman_curia/secretariatstate/documents/rc_seg-st_doc_20000211_tauran-acdlife_en.html. Patenting human genes—products of nature—is recognized as a gross violation of this common responsibility worldwide.

III. Allowing Patents of DNA Violates the Purposes of Patent and Property Law.

Allowing patents of human genetic material implicates core concerns of intellectual property law by creating a monopoly over a fruitful vein for research that should be part of the common property of all humanity. Allowing patents on basic tools of research violates both the requirement that patent law further innovation and the community purposes of property.

A. Patent law exists to encourage innovation.

The U.S. patent system is designed to incentivize research and innovation. Upholding human DNA patents harms this purpose. *See* Lori Andrews & Jordan Paradise, *Gene Patents: The Need for Bioethics Scrutiny and Legal Change*, 5 YALE J. HEALTH POL'Y L. & ETHICS 403 (2005). The proposition that human DNA is patentable defies over a century of this Court's precedent, which has repeatedly emphasized that "laws of nature, physical phenomena, and abstract ideas are not patentable subject matter," because discoveries of nature are open to study by all who would innovate for the greater good. *Chakrabarty, supra*, at 303.

This Court has consistently recognized that monopolizing natural phenomena through the grant of a patent promotes selfish gain, at the expense of innovation that can benefit everyone. *See generally Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012). This danger becomes acute when a patented process forecloses more future invention than the underlying discovery justifies. *Id.*; *see also* Mark A. Lemley et al., *Life After Bilski*, 63 STAN. L. REV. 1315 (2011).

Myriad Genetics has violated this long-held principle by claiming exclusive rights over facts of nature. Myriad Genetics has not found a unique use for DNA. Merely removing a gene from its cell and cellular components does not make it patentable subject matter. Removing the BRCA genes from the body does not significantly transform them in any way. Similar in their origins to a "new plant found in the wild;" these gene sequences occur naturally in the human body. *See Chakrabarty*, *supra*, at 309-10. This "invention" is "fit only for the same beneficial uses as theretofore." *See Am. Fruit Growers, Inc. v. Brogdex Co.*, 51 S. Ct. 328, 330 (1931) (denying a patent for borax-treated oranges where they do not gain any new functions from the treatment).

Having no practical use in isolation, genome sequences provide basic knowledge that must be interpreted and employed as a tool for future research. John Sulston, Who Owns Your Body: Nobel Laureate Opposes Gene Patents 125-27 (2006). From this natural function of human DNA it follows that the only particular "application" of Myriad's patent over the isolated DNA sequence is to further additional research on breast cancer, an enterprise dependent on collective innovation.

The proposed "application" of Myriad Genetics' isolated DNA sequence is not sufficiently useful to warrant exclusive ownership rights over human DNA and thereby foreclose others from "conventional [research] activity previously engaged in by those working in the field." *See Prometheus*, *supra*, at 1299. This Court rejected a similar application in *Prometheus* because "the grant of patents that tie up [the] use [of the underlying natural laws would] inhibit future innovation premised upon them" and would prevent "more future invention than the underlying discovery could reasonably justify." *Id.* at 1301. Upholding Myriad Genetics' patents, and thus foreclosing essential BRCA testing alternatives for breast cancer patients, harms vulnerable people. Myriad Genetics' patents cannot be "designed around" by other companies to avoid infringement. In light of the impossibility of developing and perfecting BRCA testing, the consequence of this monopoly over BRCA1 and BRCA2 will be less innovation and poorer health outcomes. *See* Sulston, *supra,* at 125-27.

B. Property should be used for the good of the community.

Humans are meant to claim property for the good of others as well as for themselves. Eight hundred years ago, Thomas Aquinas wrote that "man should not consider his material possessions as his own, but as common to all, so as to share them without hesitation when others are in need." THOMAS AQUINAS, SUMMA THEOLOGIAE II-II 66.2 (Fathers of the English Dominican Province trans., 2d ed. 1920). *available at* http://www.newadvent.org/summa/3066.htm#article2. Property rights exist to further development, especially at the service of the poor, sick, and vulnerable—"[t]hey are recognized to that end, and are limited by it." *State v. Shack*, 277 A.2d 369, 372 (N.J. 1971). Pope John Paul II described the belief that "the goods of this world are originally meant for all" as "a characteristic principle" of the Christian faith. John Paul II, *Sollicitudo Rei Socialis*, para. 42, Dec. 30, 1987, *available at* http://www.vatican.va/holy_father/john_paul_ii/encyc licals/documents/hf_jpii_enc_30121987_sollicitudo-rei-socialis_en.html. He advocated respect for the common nature of knowledge in particular, stating that "the results of research should be made available to the whole scientific community and cannot be the property of a small group." *Id.*

The property rights claimed by Myriad Genetics have not furthered innovation, and therefore have not advanced the public good. Myriad Genetics has twice used them to strong-arm its competition out of BRCA research. *See generally Myriad Genetics, Inc. v. OncorMed, Inc.*, No. 2:97-cv-0035 (D. Utah 1997); *Myriad Genetics, Inc. v. Univ. of Pa.*, No. 2:98-cv-829 (D. Utah 1998). "Ownership of this kind has no justification, and represents an abuse in the sight of God and humanity." John Paul II, *Centesimus Annus*, para. 43, May 1, 1991, *available at* http://www.vatican.va/holy_father/john_paul_ii/encyclicals/documents/hf_jp-ii_enc_01051991_centesimus-annus_en.html. While genetic research undoubtedly yields valuable scientific information and advances in health care, it must not foreclose research that could benefit society and its most marginalized members.

Myriad Genetics' financial stake in these patents and profit motive will conflict with the interests of the people with the greatest need for access to science based on genetic research. *See* Kane, *supra*, at 707. The court below failed to consider the grave consequences of allowing patent claims over human DNA—namely, the sweeping foreclosure of critical opportunities for innovation in genetic research that could help the neediest people in society. *Ass'n for Molecular Pathology v. United States PTO*, 689 F.3d 1303, 1354 (Fed. Cir. 2012).

The use of human genetic material has vast potential for people in great medical need, along with spiritual, social, and moral implications. This Court should be wary of granting ownership over the divine gift of biological components to the highest bidder, thereby excluding countless others from developing further uses for them. The gift of human genetic material more appropriately belongs to the whole species, so that it can be studied and used for everyone's gain.

IV. Myriad Genetics' Patents Harm Vulnerable People.

Granting a gene patent, in violation of the core principles described above, would be contrary to the Christian value of seeking the welfare of vulnerable people. Dwayne Hastings, a Southern Baptist, writer explains that "[i]t is scripturally incumbent upon Christians to work for the health and wholeness of all Americans, especially in light of the crisis of uninsured and underinsured Americans . . . ." Dwayne Hastings, *U.S. Health Care System in Crisis*, 1 FAITH AND FAMILY VALUES MAGAZINE 6 (2008), *available at* http://faithandfamily.com/documents/pdf/magazine/2008-1.pdf. For years, American Catholic bishops have urged the country to undertake a "new commitment to meeting the health care needs of our people, especially the poor and vulnerable." U.S. Conference of Catholic Bishops, *Health Care for All, available at* http://old.usccb.org/sdwp/national/brochure1.pdf [hereinafter *Health Care for All*]. Baptists, Catholics, and other Christians believe Jesus' words, that "God blesses those who hunger and thirst for justice, for they will be satisfied," and believe that providing access to health care is key to honoring God's will. *Matthew* 5:6 (New Living Translation).

Myriad Genetics' patents do not help sick and vulnerable people access the medical technology they need. First, Myriad Genetics' patents would place diagnostic genetic testing beyond the means of many uninsured and underinsured Americans. Second, they would prevent many people from getting a second option when faced with the threat of breast cancer. These problems raise grave ethical concerns and undermine the case for Myriad Genetics to be granted exclusionary rights over the BRCA1 and BRCA2 genes.

A. Myriad genetics' patents create barriers to health care.

The BRCA1 and BRCA2 gene sequences are associated with a significantly higher risk for breast cancer. Breast cancer is a devastating disease—in 2012 alone, nearly 230,000 new cases of invasive breast cancer were diagnosed in this country. In their lifetime, one in eight women will develop invasive breast cancer. American Cancer Society, *Breast Cancer: Key Statistics, available at* http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-key-statistics.

Myriad Genetics is the sole provider of genetic testing for the BRCA1 and BRCA2 genes in the United States by virtue of its patents. Myriad Genetics has taken advantage of the lack of competition and has driven the testing costs to a prohibitive level. Many women are unable to afford the inordinate $2,680 one of its tests costs. Cancer Institute of New Jersey, *Health Professionals Workshop Information: Case Studies*, *available at* http://www.umdnj.edu/cigenweb/health_pro/workshop.htm. ("With . . . the significant cost (currently Myriad Genetics charges $2680 for full sequencing), many patients decide on their own not to have testing."). By preventing access to an early detection test, Myriad Genetics has essentially eliminated the ability of these women to avoid even more expensive treatments for cancer in its later stages, such as mastectomies or chemotherapy.

Genetic testing itself is not inherently expensive, and several groups have expressed outrage at the prices charged by Myriad Genetics. Some have gone so far as to ignore patents held by Myriad Genetics over this information in other countries. For example, a French geneticist is now offering comparable genetic testing for significantly less. Lori Andrews, *Patents: The Need for Bioethics Scrutiny and Legal Change*, 5 YALE J. HEALTH POL'Y, L., & ETHICS 403 (2005).

As believers in Christ who healed many people in both soul and body during his ministry without asking anything in return, Christians cannot sit silently and watch Myriad Genetics make medicine too expensive for the least brothers and sisters of the human family. "It is inconceivable that a nation so blessed by God and so dedicated to the proposition that all men are created equal would allow some of its citizens" to go without access to medical technology. Hastings, *supra*, at 6. Health care is "among those basic rights which flow from the sanctity and dignity of human life"—not from the ability to pay. *Health Care for All*, *supra*, at 1.

B. Preventing alternative genetic testing techniques creates barriers to second opinions.

Every person who desires to do so should be free to obtain a second opinion when confronted with a cancer diagnosis. Myriad Genetics does not offer a complete test for all mutations associated with breast cancer, which results in a high prevalence of unclear results from their tests. Scientific peer review shows that Myriad Genetics' tests fail to detect ten to twenty percent of expected mutations in the BRCA1 mutation alone. Andrews, *supra*, at 403. This uncertainty is causes man women to have needless mastectomies or oophorectomies. *Stifling or Stimulating – The Role of Gene Patents in Research and Genetic Testing: Hearing Before the Subcomm. on Cts., the Internet and Intell. Prop. of the H. Judiciary Comm.*, 110th Cong. 47 (2007) (statement of Dr. Wendy Chung). The danger of incorrect diagnoses prompted France to challenge Myriad Genetics' patents, just as the Association for Molecular Pathology does today. Andrews, *supra*, at 403.

If this Court upholds Myriad Genetics' patents over the isolated BRCA1 and BRCA2 sequences, the availability of alternative testing techniques and medical second opinions to patients who are forced to make imperative life decisions will be restricted. Patents and licensing practices create barriers impeding access to accurate diagnostic genetic testing by removing the patient's choice. Andrew S. Robertson, *The Role of DNA Patents in Genetic Test Innovation and Access*, 9 NW. J. TECH. & INTEL. PROP. 377, 9 (2011). These harms are especially evident because the patent holder, Myriad, has issued an exclusive license, restricting all BRCA1 and BRCA2 genetic testing to a single laboratory. *Id.* Myriad Genetics' patents over the isolated BRCA sequences, by preventing second opinions and obstructing access to top-quality testing, eviscerates the breast cancer patient's access to necessary alternatives.

The harmful effects of human gene patenting can be prevented. Allowing Myriad Genetics to patent gene sequences would be devastating to patients and innovators nationwide. This Court has the opportunity to bring peace of mind to the women across the country facing a devastating disease. The invalidation of Myriad Genetics' patents will give breast cancer patients access to much-needed alternatives, which is itself a religious obligation—while preserving other vital religious values that form the foundation of the legal system in the United States.

CONCLUSION

For the foregoing reasons, amici curiae respectfully requests that this Court vacate the judgment of the Federal Circuit and reinstate the judgment of the District Court.

Respectfully submitted,

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January 31, 2013

AMICUS
CURIAE
BRIEF

Supreme Court, U.S.
FILED
MAR 14 2013
OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION OF MOLECULAR PATHOLOGY, ET AL.,
Petitioners,

v.

MYRIAD GENETICS, INC., ET AL.
Respondents.

**On Writ of Certiorari to the
United States Court of Appeals
For the Federal Circuit**

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March 14, 2013

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STATEMENT OF INTEREST

This brief is submitted by the Federal Circuit Bar Association ("FCBA") as *amicus curiae* in support of Respondents to urge the Court to affirm the judgment of the court of appeals and reject the attempt of Petitioners and certain *amici* to narrow the scope of patent eligibility under 35 U.S.C. § 101.[1] The FCBA is a national bar organization with nearly 2,500 members from all geographic areas of the country. The FCBA offers a forum for discussion of the common concerns between bar and courts, litigators and corporate counsel. One of the FCBA's purposes is to render assistance to the courts in appropriate instances, both in procedural and substantive practice areas.

The FCBA has no interest in any party to this litigation or stake in the outcome of this case. Neither the decision to file this brief nor the views articulated in it are expressive of, or binding upon, those members of the Board of Governors of the FCBA who are employees of the Federal Government.

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[1] In accordance with Supreme Court Rule 37.3(a), the FCBA states that counsel for Petitioners filed a general consent to the filing of *amicus* briefs on January 2, 2013. Respondents granted consent on March 3, 2013, via electronic mail, a copy of which has been filed with the Clerk. Pursuant to Supreme Court Rule 37.6, the FCBA states that this brief was not authored, in whole or in part, by counsel to a party, and that no monetary contribution to the preparation or submission of this brief was made by any person or entity other than the FCBA or its counsel.

SUMMARY OF ARGUMENT

The single question presented by Petitioners embeds at least five misleading assumptions. As an initial matter, the question incorrectly suggests that § 101 of the Patent Act is a catch-all provision designed to weed out patent claims that are defective for a variety of reasons, including overbreadth. In fact, that section is narrowly directed at the question of patent eligibility. Other misleading aspects of the question suggest that the Court's ruling in this case will affect only patents claiming human genes. In fact, a ruling for Petitioners would cast doubt on numerous DNA patents that are not drawn to human genes. Another misleading aspect of the question is that it suggests that all claims directed to human genes present the same issue of patent eligibility. In fact, the claims now before the Court include both full-length isolated genes as well as cDNAs, genes that are created by humans from messenger RNA transcripts. A final misleading assumption is that a gene is the same as an isolated gene. All the claims now before the Court are directed to ***isolated*** DNA molecules, which are chemically distinct from their natural counterparts and, in consequence, have tremendous diagnostic and therapeutic utility that natural genes lack. (Section I.)

Even under the narrowest interpretation of this Court's cases, claims to isolated DNA molecules are patent-eligible. They are novel, man-made creations that are chemically distinct from naturally-occurring DNA. Further, they greatly enhance the utility of the DNA in its natural form, a fact that should weigh heavily in favor of their patent-eligibility under a proper reading of 35 U.S.C. § 101. Many of Petitioners' complaints about the claims relate to asserted flaws that are unrelated to the patent-eligibility of the claims and raise issues that are not properly before the Court. (Section II.)

The questions before the Court are highly controversial and involve questions of significant medical and scientific complexity. These questions should be addressed to the political branches of government. In fact, Congress has recently considered these questions and has chosen not to make isolated genes ineligible for patenting. In enacting Section 33 of the Leahy-Smith America Invents Act, Pub. L. No. 112-29 (2011), Congress expressly declined to limit the patent eligibility of DNA molecules. Congress has also refused to pass other legislation addressing the very policy issues raised by Petitioners. (Section III.)

ARGUMENT

I. PETITIONERS' QUESTION MISLEADINGLY SUGGESTS AN INCORRECT ANSWER.

Petitioners have presented the question, "Are human genes patentable?" The question subtly suggests the wrong conclusion, because it embeds at least ***five*** misleading assumptions.

1. The first is that the relevant inquiry is about ***patentability***, not simply ***patent eligibility***. As explained in Section II.C. below, the inquiry under § 101 is confined to whether an invention or discovery is eligible for patenting at all. Whether a patent-eligible invention is "patentable," on the other hand, depends on the "conditions and requirements" of other sections of the Patent Act, as also discussed below. *See* 35 U.S.C. § 101.

2. The second misleading assumption is that there is something special about human genes, as opposed to genes of other organisms. (This case does not implicate the principle, discussed below in Section III, that a patent may not claim a whole human organism.) Many non-human genes are patented and, like human genes, are commercially important. For example, various bacterial genes are critical for the production of amino acids, and murine (mouse) genes can be used as immunological targets or probes. Petitioners' question appears to suggest that there is a conceivable basis for ruling that human genes are not patent-eligible, while leaving the question of other genes for another day. However, any ruling by this Court that human genes

are not patent-eligible logically would extend to all gene patents, not just patents drawn to human genes.

3. The third misleading assumption is that there is something special about genes, as opposed to other regions of DNA. Many DNA patents are drawn to sequences that are not genes and do not encode proteins. Nevertheless, these patents provide important protections for many innovations in the manufacturing of biologic drugs and other therapies. For example, numerous patents are drawn to control sequences of DNA, sequences that, when isolated from their natural context, can enhance production of desired therapeutic or other products. An example of such a control sequence is the promoter-regulatory region of human cytomegalovirus. In the early 1980s, a scientist at the University of Iowa isolated and patented this region, which was broadly licensed by the biotechnology industry for the production of biologic drugs. *See* U.S. Patent No. 5,385,839; *see also* University of Iowa, *Stinski to Receive UI's First Distinguished Inventor Award* (Sept. 30, 2004), http://news-releases.uiowa.edu /2004/september/093004stinski-award.html. The reasoning underlying Petitioners' arguments against gene patents apply equally to patents covering other regions of DNA. Thus, any ruling in favor of Petitioners would likely destroy any rationale for the patent eligibility of these important inventions as well.

4. The fourth misleading assumption is that the term "human genes" presents a single issue to this Court. In fact, as discussed in the Federal Circuit's

opinion, that term embraces both full-length genes having the full sequence of a corresponding natural gene, including intron sequences that do not encode amino acids; and cDNAs, which are genes obtained by manipulating messenger RNA to create a truncated gene that does not contain the natural intron sequences. *See Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 689 F.3d 1303, 1311-13 (Fed. Cir. 2012); *see also* Brief for *Amicus Curiae* Eric S. Lander in Support of Neither Party at 20-21 (hereinafter "Lander *Amicus* Brief"). Even *amicus* Eric Lander, who largely criticizes the reasoning of the Federal Circuit, agrees with that court that cDNAs are human creations that should be patent-eligible. Lander *Amicus* Brief at 21. However, the sweeping question presented by Petitioners lumps both kinds of genes into a single category. This is particularly problematic in view of the fact that several of the claims now before the Court (*e.g.*, claims 2 and 7 of U.S. Patent No. 5,747,282) are expressly drawn to cDNAs, while certain others might be interpreted as being so limited during a claim construction proceeding.

5. The fifth misleading assumption is that the claims are drawn simply to "human genes," not ***isolated*** human genes. Petitioners' question—"Are human genes patentable?"—suggests that the isolated DNA molecules of the claims are the ***same*** as genes in their natural context, and that all that differentiates one from the other is the act of "simply ... removing ... genes from the body." Pet. Br. at i. The notion that such a removal is a simple or un-inventive process is untrue.

As an initial matter, the process of isolation requires the application of some of the most groundbreaking technologies developed in the 20th century. These technologies enable the extraction of nucleic acids from cells, the cutting of nucleic acids into fragments, the analysis of the nucleotide sequence and functions of those fragments, the replication or synthesis of nucleic acid molecules, and the transfer of such molecules into plasmids or other vehicles for their storage and use.

Early projects to isolate human genes required months of painstaking laboratory work. Indeed, isolating a gene is a misnomer for the lengthy experimental process required. The process is not a simple extraction or purification, but rather a complex series of steps to create an isolated DNA molecule having the same genetic information as—but a different chemical structure from—a natural DNA of interest. Those steps, at least in the early years of isolating genes, included the extraction of undifferentiated RNA molecules from cells, the creation of cDNA molecules corresponding to those RNA molecules, the insertion of the cDNA molecules into plasmids after engineering both the cDNA molecules and the plasmids so that the insertion could be performed, the transformation of thousands or millions of bacterial cells with those plasmids, the production of polypeptides using those cells, the search for polypeptides bearing desired characteristics from among thousands of polypeptides produced by the cells, the sequencing of DNA fragments from cells producing the desired polypeptides, and the combining of separate sequenced fragments into a full-length isolated DNA molecule. The starting materials were RNA molecules extracted from cells, not chromosomal DNA, and the specific DNA molecules investigated were cDNAs constructed using RNA. *See, e.g.,* R. Derynck et al., *Isolation and Structure of a Human Fibroblast Interferon Gene,* Nature 285:542 (1980); J.T. Wilson et al., *Insertion of Synthetic Copies of Human Globin Genes Into Bacterial Plasmids,* Nucleic Acids Res. 5:563 (1978). As discussed above, such cDNAs are human creations and lack the non-coding DNA found in natural, chromosomal DNA.

While the processes for isolating genes became easier and were simplified over time, they still are anything but an elementary process of extraction or purification. For example, Myriad's inventors used techniques of genetic analysis to identify regions of chromosomal DNA associated with cancer. They isolated the genes of interest by analyzing a massive library of different cDNAs (again, created from RNAs, and thus different from chromosomal DNA) to find cDNAs associated with the suspect regions. They performed further sequencing analysis to identify the cDNAs having suspicious mutations in cancer patients, and they combined separate fragments of the genes of interest into full-length isolated DNA molecules.

Further, as the Federal Circuit made clear in its opinion, isolated DNA molecules are not natural phenomena. Once a gene has been isolated, it is a new and different chemical entity that is critically different from natural, chromosomal DNA. *Ass'n for Molecular Pathology*, 689 F.3d at 1328 ("Isolated

DNA has been cleaved (i.e., had covalent bonds in its backbone chemically severed) or synthesized to consist of just a fraction of a naturally occurring DNA molecule.").

Amicus Eric Lander takes issue with the Federal Circuit's scientific premise, observing that DNA fragments may be found in the body separate from the chromosomes in which they originated. Lander's argument is carefully worded so as not to highlight its central flaw: that the DNA fragments that can be found in the body as a result of such processes as cell death are not cleaved exactly at the beginning or end of genes, but occur as random fragments. Thus, Lander argues that naturally occurring DNA fragments may "cover" the BRCA1 and BRCA2 genes. Lander *Amicus* Brief at 16. However, a large fragment that happens to include one of the genes of interest must still be cleaved—chemically altered—so as to yield the gene of interest. Smaller fragments must be joined to create a full-length gene. The fact that cells contain random DNA fragments also overlooks the difficulty, discussed above, of locating and identifying any particular DNA fragment, cleaving out a desired gene, and understanding what function its pieces may have and what parts may be missing from it. Thus, referring to a random, naturally occurring fragment as an "isolated" DNA assumes what must, but cannot, be shown: that a naturally occurring DNA fragment is the same as a gene that has been isolated from a natural context.

Petitioners attempt to paper over the fact that isolated genes differ from naturally occurring ones by arguing that "the gene sequence, the information it includes, and the laws it embodies are the same whether in or out of the body." Pet. Br. at 9. However, the fact that DNA has a sequence does not mean that an isolated DNA ***molecule*** consists only of its sequence. Its other chemical attributes are critically important to its utility, which is why an isolated gene is simply not the same thing, or even a purified version of the same thing, as the chromosomal DNA to which it corresponds in sequence.

Petitioners' argument is like arguing that a novel drug compound is not entitled to patent protection because the elements by which it is constituted (oxygen, hydrogen, carbon, etc.) still have all the same protons, neutrons, and electrons that they have in nature. Such an argument is clearly wrong, but it is analytically indistinguishable from the argument Petitioners present to this Court. The Court should reject this oversimplified analysis.

II. ISOLATED DNA IS PATENT-ELIGIBLE UNDER § 101 OF THE PATENT ACT.

The FCBA urges the Court to rule that isolated genes are eligible for patenting. Section 101 of the Patent Act, 35 U.S.C. § 101, defines the inventions and discoveries eligible for patent protection:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a

> patent therefor, subject to the conditions and requirements of this title.

Isolated human genes are new and very useful compositions of matter and should be eligible for patent protection if claims drawn to them satisfy the other statutory requirements for patentability.

A. Isolated DNA Is Patent-Eligible Even Under the Narrowest Reading of This Court's Precedents.

This Court's cases addressing 35 U.S.C. § 101 have recognized that Congress intended the threshold patent-eligibility standard set forth in that section of the Patent Act to be construed broadly. *J.E.M. Ag. Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 130 (2001) ("the language of § 101 is extremely broad") (citing *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980)). Congress used "expansive terms" in defining the four categories of inventions eligible for patent protection under § 101: processes, machines, manufactures, and compositions of matter. *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010) (quoting *Chakrabarty*, 447 U.S. at 308). In *Bilski*, this Court expressly noted that by using the comprehensive modifier "any," Congress "plainly contemplated that the patent laws would be given wide scope" and explained that "Congress took this permissive approach to patent eligibility to ensure that ingenuity should receive a liberal encouragement." *Id.*

However, this Court has also made clear that neither "laws of nature" nor "products of nature" are patent-eligible under § 101. *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. __, 132 S. Ct. 1289, 1293 (2012); *Chakrabarty*, 447 U.S. at 309. The Court's recent ruling in *Mayo* disapproved as "effectively claim[ing] the underlying laws of nature" a patent claim directed to determining blood levels of certain metabolites. 132 S. Ct. at 1305. Specifically, the claim was drawn to "determining" the level of resulting metabolites in the subject's blood, "wherein" a level below a certain threshold "indicate[d] a need" to increase the dose, while a level above another threshold "indicate[d] a need" to reduce the dose. *Id.* at 1295. In holding that these claim elements were "not sufficient to transform unpatentable natural correlations into patentable applications of those regularities," the Court explained that "the claims inform a relevant audience about certain laws of nature; any additional steps consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately." *Id.* at 1298.

The Prometheus claims, with their almost passive observation of metabolite levels, stand in stark contrast to claims drawn to isolated DNA molecules. As discussed above in Section I, obtaining such a molecule requires significant human activity and results in a product that is not found in nature. In this respect, claims drawn to isolated DNA molecules are akin to the claims of "a typical patent on a new drug," a type of claim that the Court contrasted favorably with the Prometheus claims. *Id.* at 1302. The massive human effort required to isolate or synthesize DNA molecules is completely unlike the passive observation of a natural relationship.

The *Mayo* decision has little relevance to claims drawn to isolated DNA molecules in any event, because those present a different issue: whether such molecules are patent-eligible "composition[s] of matter" or ineligible "products of nature." Thus, their patent eligibility is governed by this Court's prior cases on products of nature, two of which are particularly on point: *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948) and *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

In *Funk Brothers*, just as in *Mayo*, the inventor discovered a natural phenomenon: that certain strains of nitrogen-fixing bacteria, in contrast to the norm, did not exhibit a mutually inhibiting effect on each other. 333 U.S. at 130. Thus, those select strains could be used together to obtain superior nitrogen fixation. The Court held that claims drawn to a mixture of mutually non-inhibitory bacteria were not patent-eligible, however, because each strain, and the mixture, were "the work of nature." *Id.* The problem with the claims was that, while they exploited a discovery about the qualities of the bacteria, they did not add anything to the natural phenomenon the inventor had observed: "[P]atents cannot issue for the discovery of the phenomena of nature." *Id.*

Claims to an isolated DNA molecule, on the other hand, resemble the claims held by this Court to be patent-eligible in *Chakrabarty*. There, as in *Mayo* and *Funk Brothers*, the inventor discovered a natural phenomenon—that certain naturally occurring DNA plasmids (circular DNA molecules naturally present in bacteria) encoded enzymes capable of degrading oil. *Chakrabarty*, 447 U.S. at 305-06. Just as the *Funk Brothers* inventor reasoned that it would be advantageous to bring together multiple strains of nitrogen-fixing bacteria, Chakrabarty reasoned that bringing together several of the oil-degrading plasmids would be advantageous. Accordingly, Chakrabarty created a new organism that incorporated several of the oil-degrading plasmids. What distinguished Chakrabarty's creation from the *Funk Brothers* mixture was that Chakrabarty had created a new organism not found in nature. *Id.* at 309-10.

Claims to isolated DNA molecules are patent-eligible, just like the new microorganisms in *Chakrabarty*, because they are novel creations that are chemically different from naturally-occurring DNA. The claim that isolating a gene is like "snapping a leaf from a tree," *see Ass'n for Molecular Pathology*, 689 F.3d at 1352 (Bryson, J. dissenting), is untrue, because the leaf remains a leaf, while an isolated gene is, as a matter of chemistry, not the same as a gene in natural context. As the Federal Circuit explained, chromosomal DNA is "intertwined with various proteins, including histones, to form a complex tertiary structure known as chromatin[.]" *Id.* at 1328. Random fragments of DNA, as discussed in Section I, are also not isolated genes, which have "been cleaved (*i.e.*, had covalent bonds ... chemically severed) or synthesized to consist of just a fraction of a naturally occurring DNA molecule." *Id.*

Thus, isolated DNA molecules are fundamentally unlike the purified, naturally-occurring chemicals found not to be patent-eligible in a series of appeals court cases. *See, e.g., Gen. Elec. Co. v. De Forest Radio Co.*, 28 F.2d 641 (3d Cir. 1928) (purified tungsten not patent eligible); *In re Marden*, 47 F.2d 957 (C.C.P.A. 1931) (purified uranium not patent eligible); *In re Marden*, 47 F.2d 958 (C.C.P.A. 1931) (purified vanadium not patent eligible); *In re Merz*, 97 F.2d 599 (C.C.P.A. 1938) (purified ultramarine not patent eligible). Petitioners cite these "purification cases" for the proposition that "courts must examine whether the composition and any characteristics specified in the claims were invented by the patentee or were the work of nature." Pet. Br. at 39. What differentiates isolated DNA molecules from DNA in nature is that they have a distinct chemical structure that enables them to be used for diagnostic and therapeutic purposes, among other things. Further, as discussed in Section I, a gene is not typically isolated by simply extracting it from the entire genome of the source organism, as one might pluck a leaf from a tree.

Isolated genes are also fundamentally unlike the borax-treated fruit ruled patent-ineligible in *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1 (1931). There, the Court reasoned that treating the fruit rind with borax did not impart to the fruit "a new or distinctive form, quality, or property.... There is no change in the name, appearance, or general character of the fruit." *Id.* at

11-12. The problem with the treated fruit claims was that the addition of borax to the rind did not effect a meaningful alteration from the natural fruit itself. The fruit was no more patent-eligible when treated with borax than it would have been when packaged in cellophane. Isolated genes, however, involve much more than a simple addition to a product of nature. As discussed in Section I, they are new molecules created by human intervention.

Thus, isolated genes are patent-eligible under the principles established in *Chakrabarty* and are fundamentally unlike the products of nature ruled patent-ineligible in *Funk Brothers*, the purification cases, and *American Fruit Growers*.

B. This Court's Prior Cases Do Not Support the Narrow, Rigid Test Proposed by Petitioners.

Citing *Chakrabarty*, 447 U.S. at 303, Petitioners urge this Court to hold that for a composition of matter to be patent-eligible, it ***must*** have "a distinctive name, character and use" and must also have "markedly different characteristics from any found in nature." Pet. Br. at 28-29. Although as set forth above, Petitioners misapply *Chakrabarty*, Petitioners' argument also fails in another crucial respect: nowhere does *Chakrabarty* hold that it sets forth the ***only*** test for patentability of compositions of matter under § 101. The Court in *Chakrabarty* simply held that because the bacteria there ***were*** markedly different from any found in nature, they ***were*** patent-eligible. *Chakrabarty* did not establish that a composition that is ***not*** "markedly different" from its natural antecedents is ***not*** patent-eligible. Indeed, *Chakrabarty* did not establish any kind of rigid or exclusive test.

Rather, *Chakrabarty* emphasized that "[i]n choosing such expansive terms as 'manufacture' and 'composition of matter,' modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope." *Id.* at 308; *see also id.* at 315 ("The subject-matter provisions of the patent law have been cast in broad terms[.]"). The Court "cautioned that courts should not read into the patent laws limitations and conditions which the legislature has not expressed." *Id.*

The Court sounded the same theme in *Bilski*, in observing that courts should avoid "adopting categorical rules that might have wide-ranging and unforeseen impacts." 130 S. Ct. at 3229. In *Bilski*, this Court rejected the Federal Circuit's "machine or transformation" test as the "sole" test for patent eligibility of process patents. Repeating its caution in *Chakrabarty* that courts should not read limitations into the Patent Act that were not expressed by Congress, the Court held that "adopting the machine-or-transformation test as the sole test for what constitutes a process ... violates ... statutory interpretation principles." *Id.* at 3226.

Applying the "markedly different" test as the exclusive basis for determining the patent eligibility of compositions of matter would also violate those principles. In fact, there is no meaningful difference between the rigid and exclusive tests advocated by

Petitioners and the machine-or-transformation test that this Court has already rejected. *See id.* 3226-27. Petitioners' arguments for the exclusive adoption of the factors articulated in *Chakrabarty* ignore this Court's guidance in *Bilski*.

Indeed, this Court's patent cases, including those concerning issues other than patent eligibility, have repeatedly emphasized that narrow and rigid tests are particularly clumsy tools for assessing human innovation. "The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 419 (2007). In *KSR*, just as in *Bilski*, this Court rejected a narrow, rigid test. 550 U.S. at 415 ("We begin by rejecting the rigid approach of the Court of Appeals. Throughout this Court's engagement with the question of obviousness, our cases have set forth an expansive and flexible approach[.]"). This Court should not begin to impose a rigid and inflexible test in the one area—patent eligibility under § 101—where Congress has unambiguously mandated breadth and flexibility.

Petitioners' inflexible approach also ignores the utility of isolated genes compared with natural DNA. Utility is a factor that this Court has pointed to in determining that an invention was patent-eligible. In *Funk Brothers*, for example, the Court pointed out that mixing the bacterial strains produced "no enlargement of the range of their utility." 333 U.S. at 131. The Court continued:

> Each species has the same effect it always had. The bacteria perform in their natural

> way. Their use in combination does not improve in any way their natural functioning. They serve the ends nature originally provided and act quite independently of any effort of the patentee.

Id. Thus, the inquiry should focus not only on the narrow criteria advanced by Petitioners, but also on differences in utility, and the fact that the intervention of humans created those differences. *See Chakrabarty*, 447 U.S. at 310 (in ruling transformed bacteria patent-eligible, noting their "potential for significant utility").

The isolation of a human gene allows it to be used to diagnose and treat diseases—uses to which it could not be put in its natural context. Petitioners concede that natural genes lack the utility of an isolated DNA molecule: "It is not currently possible to use genes, including looking at or sequencing them, without removing or 'isolating' them from the body." Pet. Br. at 9. This increase in utility results from human ingenuity and strongly suggests that isolated genes should be patent-eligible.

C. Although Isolated DNA is Eligible for Patenting, Other Statutory Restrictions on Patentability Still Apply.

Patent eligibility under § 101 is only one of many hurdles that a patent claim must surmount in order to be deemed worthy of patent protection. As this Court stated in *Bilski*, "The § 101 patent-eligibility inquiry is only a threshold test." 130 S. Ct. at 3225. As the language of § 101 expressly acknowledges, other "conditions and requirements" of the Patent Act must also be met, including novelty (35 U.S.C. § 102), non-obviousness (§ 103), written description (§ 112), and enablement (§ 112). The limitations found in §§ 102, 103, and 112 "serve a critical role in adjusting the tension, ever present in patent law, between stimulating innovation by protecting inventors and impeding progress by granting patents when not justified by the statutory design." *Bilski*, 130 S. Ct. at 3229. As Justice Stevens cautioned in his concurrence in *Bilski*:

> Given the many moving parts at work in the Patent Act, there is a risk of merely confirming our preconceived notions of what should be patentable or of seeing common attributes that track the familiar issues of novelty and obviousness that arise under other sections of the statute but are not relevant to § 101.

Id. at 3238 (internal quotation marks and citation omitted).

In their brief, Petitioners fall right into the trap identified by Justice Stevens. For example, Petitioners argue that that the claims are overbroad, because they cover many different forms of the genes of interest: "The challenged claims cover all isolated forms of the naturally-occurring genes, whether previously identified or not." Pet. Br. at 41. Similarly, Petitioners argue that the Myriad patents "undermine the patent system by giving Myriad the right to any applications of isolated DNA without disclosing them or even having done the work to develop them." *Id.* at 41.

Insofar as Petitioners' criticisms of the claims are correct, the claims can be challenged under the provisions of the Patent Act that protect against overly broad claims, such as 35 U.S.C. §§ 102, 103, and 112. Broad claims that encompass prior art run afoul of §§ 102 or 103. Claims that are overly broad compared to the inventors' actual discoveries are invalid for lack of written description under § 112. If the Myriad claims are overbroad, the solution is not to rule that all isolated genes are ineligible for patenting under § 101.

Petitioners react with outrage to the practical consequences of Myriad's patent monopoly. However, many of the problems Petitioners point to are illusory. Statutory and judicial exemptions to patent infringement protect many of the activities that Petitioners complain are being blocked by the Myriad patents. For example, uses of the patented technology may be protected if they are connected with seeking regulatory approval or are experimental. *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 206 (2005); *Madey v. Duke Univ.*, 307 F.3d 1351, 1362 (Fed. Cir. 2002).

Petitioners' policy arguments that the Myriad patents block the development of "drugs, instruments, and treatment methods," Pet Br. at 44, completely ignore the critical importance of patent protection in the biotechnology industry. Many biotechnology drugs, including insulin (used to treat diabetes), human growth hormone (for growth hormone deficiency), erythropoietin (for anemia), beta-interferon (for multiple sclerosis), and beta-glucocerebrosidase (for Gaucher's disease) are or were protected by gene patents. A ruling that gene patents are invalid would throw the industry into turmoil and would threaten the development of new "drugs, instruments, and treatment methods."

Indeed, Petitioners' arguments suggest a thoroughgoing disagreement with the patent system itself. However, § 101 should not be gutted simply because Petitioners disagree with the balance between innovation and monopoly established in Article I of the Constitution and by Congress.

In sum, claims drawn to isolated DNA molecules should "at the very least not [be] barred at the threshold by § 101." *Diamond v. Diehr*, 450 U.S. 175, 188 (1981). Whether such claims also meet the conditions of patentability imposed by §§ 102, 103, and 112 are questions that are not before the Court.

III. THE COURT SHOULD DEFER TO CONGRESS' POLICY CHOICE DECLINING TO LIMIT PATENT ELIGIBILITY OF GENES.

Congress has considered the patent eligibility of genes, including human genes, and has declined to limit their eligibility. Instead, Congress has made the policy choice that only human ***organisms*** should be patent-ineligible. Under Section 33 of the Leahy-Smith America Invents Act of 2011 ("AIA"), Congress limited the broad scope of § 101 to specifically exclude human organisms: "Notwithstanding any other provision of law, no patent may issue on a claim directed to or encompassing a ***human organism***." Pub. L. No. 112-29 (2011) (emphasis added). Although Congress specifically considered the issue, as discussed below, it did not prohibit issuing patents on genes, including human genes.

Section 33 of the AIA, generally known as the Weldon Amendment, is derived from a series of amendments to appropriations bills since 2004. *See* 157 CONG. REC. E1177 (daily ed. June 23, 2011) (statement of Rep. Christopher Smith). *See generally* Joe Matal, *A Guide to the Legislative History of the America Invents Act: Part I of II*, 21 FED. CIR. B.J. 435, 510-11 (2011) (detailing legislative history of Section 33). Notably, in floor debate introducing his amendment, Representative Weldon explained that "I recognize that there are many institutions ... that have extensive patents on human genes, human stem cells. This would not affect any of those currently existing patents." 149 CONG. REC. 18998 (July 22, 2003) (statement of Rep. Weldon.); 149 CONG REC. H7274 (daily ed. July 22, 2003).[2]

Section 33 of the Leahy-Smith America Invents Act was itself introduced as an amendment to the AIA by one of its lead sponsors, Rep. Lamar Smith, the then-Chairman of the House Judiciary

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[2] These floor statements were incorporated as part of the Congressional Record accompanying the consideration of Section 33 of the AIA. 157 CONG. REC. E1177-1178 (daily ed. June 23, 2011) (statement of Rep. Christopher Smith) (submitting statements by Rep. Weldon into legislative record).

Committee, and the Representative after whom the AIA is named. 157 CONG. REC. H4451 (daily ed. June 22, 2011); *see also* Matal, *supra*, at 510-11. In supplemental remarks on behalf of the Committee on the Judiciary regarding the proposed amendment that eventually became Section 33 of the AIA, Chairman Smith explained:

> The Committee recognizes that the economic viability of the biotechnology industry requires that patents be available for the full spectrum of innovations that may be subject to commercialization. ... The Committee also recognizes that continued innovation in the biomedical and biotechnological fields will lead to new kinds of inventions, and it expects that the overwhelming majority of such inventions will not raise any of the concerns that the present legislation addresses. In particular, nothing in this section should be considered to limit the ability of the PTO to issue a patent containing claims directed to or encompassing: 1. Any chemical compound or composition, whether obtained from animals or human beings or produced synthetically, and whether identical to or distinct from a chemical structure as found in an animal or human being, including but not limited to nucleic acids ....

157 CONG. REC. E1183 (daily ed., June 23, 2011) (statement of Rep. Lamar Smith); *see also* Matal, *supra*, at 510-11.

The enactment of Section 33 of the AIA came just a few years after Congress considered, and rejected, much broader legislation, the Genomic Research and Accessibility Act ("GRAA"), that sought to make all genes patent-ineligible. The GRAA, introduced in 2007, provided that "no patent may be obtained for a nucleotide sequence, or its functions or correlations, or the naturally occurring products it specifies." H.R. 977, 110th Cong. (2007). Thus, it would have enacted exactly what Petitioners want: to withdraw patent eligibility for all genes and other DNA molecules, regardless of source. In remarks introducing the legislation, the bill's sponsor raised many of the policy issues that Petitioners raise before this Court regarding gene patents.[3] 153 CONG. REC. E316 (daily ed. February 9, 2007) (statement of Rep. Becerra).

Congress declined to strip isolated DNA of patent eligibility and did not pass the GRAA. Understood together, the fates of Section 33 of the AIA (which was passed into law) and the GRAA (which was not) indicate that whole human organisms are not patent-eligible, but isolated DNA is. The legislative history of Section 33 of the AIA confirms this intent. 157 CONG. REC. E1183 (daily ed. June 23, 2011) (statement of Rep. Lamar Smith).

Now that Congress has spoken, this Court should not read into the broad language of § 101 further limitations that were considered, and rejected, by Congress. *See Andrus v. Glover Constr. Co.*, 446 U.S. 608, 616-17 (1980) ("Where Congress explicitly enumerates certain exceptions to a general prohibition, additional exceptions are not to be implied, in the absence of evidence of a contrary legislative intent."). As this Court wisely advised less than a decade ago:

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[3] He also thanked Petitioner Association of Molecular Pathology for its support for the bill. 153 CONG. REC. E316 (daily ed. February 9, 2007) (statement of Rep. Becerra).

> There is a basic difference between filling a gap left by Congress' silence and rewriting rules that Congress has affirmatively and specifically enacted. [This Court's] unwillingness to soften the import of Congress' chosen words even if we believe the words lead to a harsh outcome is longstanding. It results from deference to the supremacy of the Legislature[.]

Lamie v. U.S. Trustee, 540 U.S. 526, 538 (2004).

The complex medical and scientific issues at stake here, and the extensive disagreement among the scientific and medical community regarding the wisdom of gene patenting, further counsel that this Court should proceed cautiously and defer to Congressional judgment. "[W]hen a legislature undertakes to act in areas fraught with medical and scientific uncertainties, legislative options must be especially broad and courts should be cautious not to rewrite legislation." *Kansas v. Hendricks*, 521 U.S. 346, 360 n.3 (1997) (quoting *Jones v. United States*, 463 U.S. 354, 365 n.13 (1983)).

This Court has declined similar invitations to engraft its political or prudential views onto Congressional statutes. In *United States v. Rutherford*, 442 U.S. 544 (1979), for example, terminally ill cancer patients sought an exception to the premarketing approval requirements under the Federal Food, Drug, and Cosmetic Act ("FD&C Act"). Specifically, the plaintiffs sought to exempt drugs used to treat terminally ill patients from the FD&C Act's regulatory requirements. *Id.* at 548-49. The lower courts agreed with the patients' arguments despite Congressional silence on the issue. *Id.* at 550-51, 554.

This Court reversed, explaining that "[u]nder our constitutional framework, federal courts do not sit as councils of revision, empowered to rewrite legislation in accord with their own conceptions of prudent public policy." *Id.* at 555. "Only when a literal construction of a statute yields results so manifestly unreasonable that they could not fairly be attributed to congressional design will an exception to statutory language be judicially implied." *Id.* This Court should follow its previous reluctance to read moral or political judgments into broadly worded statutes such as § 101 of the Patent Act. *See Chakrabarty*, 447 U.S. at 308 ("We have also cautioned that courts should not read into the patent laws limitations and conditions which the legislature has not expressed.").

In *Rutherford*, this Court was particularly careful not to reach past the FDA, the agency charged with implementing the FD&C Act. 442 U.S. at 553 ("[T]his Court has often recognized the construction of a statute by those charged with its administration is entitled to substantial deference."). In fact, the Court ruled that deference "is particularly appropriate where, as here, an agency's interpretation involves issues of considerable public controversy, and Congress has not acted to correct any misperception of its statutory objectives." *Id.* at 554. "Once an agency's statutory construction has been fully brought to the attention of the public and the Congress, and the latter has not sought to alter that interpretation although it has amended the statute in other respects, then presumably the legislative intent has been correctly discerned." *Id.* at 554, n.10; *see also Bob Jones Univ. v. United States,* 461 U.S. 574, 600 (1983) (declining to overturn agency interpretation of statute in view of unsuccessful legislation and Congress' "prolonged and acute awareness of so important an issue").

This case presents precisely the same kind of situation. As the Court counseled in *Chakrabarty*, "Whatever their validity, the contentions now pressed on us should be addressed to the political braches of the Government ... and not to the courts." *Chakrabarty*, 447 U.S. at 317.

CONCLUSION

For the reasons discussed above, the FCBA urges this Court to affirm the judgment of the court of appeals and reject the attempt of Petitioners' and certain *amici* to narrow the scope of patent eligibility under § 101.

Respectfully submitted,

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March 14, 2013

AMICUS
CURIAE
BRIEF

RECORD
AND
BRIEFS

Supreme Court, U.S.
FILED
JAN 3 0 2013
OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF *AMICUS CURIAE* FÉDÉRATION INTERNATIONALE DES CONSEILS EN PROPRIÉTÉ INTELLECTUELLE IN SUPPORT OF NEITHER PARTY

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INTEREST OF THE *AMICUS CURIAE*.[1]

Pursuant to Supreme Court Rule 37.2(a) Fédération Internationale Des Conseils En Propriété Intellectuelle ("FICPI") submits this brief as *amicus curiae* in support of neither party.

Established in 1906, FICPI is a Switzerland-based international and non-political association of approximately 5,000 intellectual property attorneys from over eighty countries, including the United States. *See* About FICPI, http://www.ficpi.org/aboutframe.html (follow "History-Future" hyperlink) FICPI's members are in private practice and their clients include individual inventors as well as large, medium and small companies. Both applicants for IP rights and entities concerned about potential infringement of the claimed subject matter are represented. One of the members' major roles is to advise inventors in intellectual property matters and secure protection for industrial innovation. FICPI supports predictable, balanced global protection of patents, the global harmonization of substantive patent law, and the interests of inventors and the U.S. Patent and Trademark Office (the "PTO") in recognizing a fair scope of patent protection consistent with the claimed invention.

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1. Pursuant to this Court's Rule 37.2(a), all parties have consented to the filing of this brief. Letters evidencing such consent have been filed with the Clerk of the Court. Pursuant to Rule 37.6, *Amicus Curiae* affirms that no counsel for any party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *Amicus Curiae*, its members, or its counsel made a monetary contribution to its preparation or submission.

FICPI recognizes that the instant case has significant potential to impact the patentability of a potentially broad class of subject matter.

Specifically, FICPI is concerned that research and valuable university and private company work in the areas of gene expression and genetic engineering applied science to solving major, catastrophic illnesses must be protected.

Furthermore, FICPI is concerned that the application of the principles announced in the Court's *Mayo* decision in this case, will negatively affect the so far very clear distinction between composition of matter claims and method claims in case law.

Because FICPI is largely comprised of patent practitioners representing both foreign and domestic inventors and corporate entities, FICPI is poised to give the court the perspective of the international patent community. In this vein, FICPI desires to ensure that its members' clients are afforded fair opportunities with respect to patenting their inventions in the United States and, therefore, respectfully submits this brief in support of neither party.

INTRODUCTION

On November 30, 2012, this court granted the petition for a writ of certiorari limited to the question 1 presented by the petition:

"Are human genes patentable?"

The challenged composition claims cover two isolated human man made genes BRCA1 and BRCA2 and certain alterations, or mutations in these genes associated with a predisposition to breast and ovarian cancers.

SUMMARY OF ARGUMENT

The issue presented is the patentability of human gene expression.

The Genes BRCA1/2 are patentable. The claims are related to isolated DNA molecules which are obtained in a laboratory and not found in nature. The isolated DNA has a markedly different chemical structure compared to native DNA. Isolating the genes from human DNA is not a natural phenomenon. It is a human accomplishment for which a protection has to be rewarded.

Mayo v. Prometheus has no bearing on Myriad. Mayo addresses patent method claims and not compositions of matter. The patent eligibility in Mayo has no application to the composition claims in Myriad and the criteria for patent eligibility of compositions was not reviewed or reserved in Mayo by this Court.

This Court's prior judgment also remains unaffected under *Mayo v. Prometheus* and has no impact on the Federal Circuit's prior judgment. The Federal Circuit concluded properly that in Myriad the composition claims cover molecules that are "markedly different" from molecules that exist in nature. Its decision was also made in accordance with the longstanding practice of the PTO.

ARGUMENT

I. THE GENES BRCA1/2 ARE PATENTABLE

Concerning the Patent-eligibility under the patent Act 35 U.S.C. 101, the Court's precedents provide three judicially created exceptions to 101 principles: "Laws of nature, natural phenomena and abstract ideas". Considering the isolated genes BRCA 1/2 it appears that the Court is dealing with a natural product but it has been isolated by the work of man.

Evaluating its patent-eligibility it is necessary to consider each individual case. The claims of the patents before us relate to isolated DNA molecules[2]. Those are not found in nature. Rather, they are obtained in laboratory and are man-made. To consider this case in a proper light it is essential to examine the idea why products of nature and laws of nature shouldn't be patent-eligible.

Through a patent, useful inventions are encouraged since the inventor's right to exclude others from making, using, offering for sale or selling his invention is protected.

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[2] The term "isolated", which is used in the claims of the patents, does not mean "purified". The claimed genes are in fact not present in the human body in admixture with other substances; they cannot be purified from any naturally existing mixture. To the contrary, they are a portion of a larger molecule, i.e. the DNA of human chromosomes, to which they are chemically bound. Consequently, in order to be obtained in the claimed "isolated" form, either they must be cleaved from chromosomal DNA or they must be synthesized; but human intervention is necessary in both cases; and such an intervention creates a new molecule which did not and does exist in nature as such.

Therefore, a natural product or a law of nature is not patent-eligible because no one invented it or should be privileged by having a patent issued.

The isolated DNA molecules before us are made from natural materials like mostly all other inventions. Nevertheless, it has a markedly different chemical structure compared to native DNAs. The isolation of the genes from the native DNA for use in the fight against breast and ovarian cancer is a significant human achievement and accomplishment. It's a scientific advance in the fight against breast and ovarian cancer. Indeed, it is necessary to differentiate between achievements produced out of natural material by using a great scientific effort and natural products or laws of nature which have just been found out by coincidence and are just described or existed before in the exact same way.

Isolating the before mentioned genes from human DNA is not a natural phenomenon. There will never be an isolated gene like the disputed ones found in nature. It is an achievement in molecular biological science. Hence, a protection of this accomplishment for the process in finding and isolating the molecules has to be rewarded. The alternative will be less activity in science.

II. *MAYO v. PROMETHEUS* HAS NO BEARING ON *MYRIAD*

Moreover, the Federal Circuit was right in its finding that *Mayo vs. Prometheus* has no bearing on the present case. The decisions are not comparable:

A. *Mayo* Addresses Patent Method Claims, Not Compositions of Matter.

In *Mayo*, this Court concluded that a three-step process to help doctors who treat patients with autoimmune diseases to determine the correct dosage of thiopurine drugs according to the patient's metabolite level is not patent eligible. This Court held that such a method simply sets forth laws of nature and does not fulfill the requirements of a transformation of unpatentable natural laws into an application that rewards inventions.

This three-step process, however, is clearly not what this Court has defined as a "composition of matter," which is one of the broad categories of patent eligible subject matter. According to this Court, a "composition of matter" includes "all compositions of two or more substances and all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids." *Diamond v. Chakrabarty*, 447 U.S. at 308 (1980). This Court identifies *Mayo* to be a case concerning "patent claims covering processes". *Mayo* at 1293.

B. Mayo has no Application to *Myriad*, other than to Restate General Principles of Patent Eligibility.

As different tests have been applied by the courts over the years for compositions as compared to method claims when examining the claims' patent eligibility, a different line of case law has been developed for each of the claim types. There is a continuous line of cases by the courts and the PTO concerning composition claims, which all follow this Court's patent eligibility test for compositions.

According to the test, only those compositions that human intervention has given "markedly different" or "distinctive" characteristics are patent eligible, whereas other compositions that, even if combined or altered in a manner not found in nature, have similar characteristics as in nature, are not patentable. *Hartranft v. Weigmann*, 121 U.S. at 615 (1887); *American Fruit Growers v. Brodgdex Co.*, 283 U.S. 1, 11 (1931). The claimed compositions in *Myriad* more than adequately meet this test for patent eligibility for a composition. The patent eligibility analysis in Mayo has no application to the composition claims in *Myriad*.

C. The Criteria for Patent Eligibility of Compositions Was Not Reviewed, Much Less Reversed, in *Mayo*.

This Court in *Mayo* cites prior composition claim cases such as *Chakrabarty* only as a reference for the very general principle that "laws of nature, natural phenomena, and abstract ideas" are not patentable under 35 U.S.C. 101, which is applicable regardless of whether the patent claims a method or a composition of matter. *Mayo* at 1293.

On the other hand, to answer the core issue of whether or not the process in question is patent eligible, this Court takes under consideration two prior cases, *Diamond v. Diehr*, 450 U.S. 175 (1981) and *Parker v. Flook*, 437 U.S. 584 (1978), that are described as "controlling precedents." Both *Diehr* and *Flook* concern method claims and not composition claims. *Mayo* at 1298. In *Diehr*, the patent claim concerned a process for molding rubber. In *Flook* it concerned a process for adjusting alarm limits in catalytic conversion of hydrocarbons.

The Mayo decision makes clear the composition-mattered distinction that exists between composition case law and method case law. This Court unequivocally decided the case according to prior method claim case law. Accordingly, there is no reason for the method claim case law in *Mayo* to be applied on the composition claims in *Myriad*, as the dichotomy was recognized by this Court in *Mayo* itself. There is simply no common ground between the two (except for the very general principles mentioned above) which would allow the application of the method claim rules reaffirmed in *Mayo* to the examination of the composition claims in *Myriad*.

For the above reasons, *Mayo* does not shed any light on *Myriad*. There is no reason for this Court to consider *Mayo* in *Myriad* as far as the question of patent eligibility of isolated DNA is concerned.

III. THIS COURT'S PRIOR JUDGMENT ABOUT PATENT ELIGIBILITY REMAINS UNAFFECTED UNDER *MAYO v. PROMETHEUS*

As shown above, *Mayo* does not have an impact on the Federal Circuit's prior judgment that the isolated DNA composition claims of the '282 patent are patent-eligible.

Under the framework set out by this Court's decision in *Chakrabarty* for deciding patent eligibility, the Federal Circuit decided that isolated DNAs have surpassed the line of being mere compositions having similar characteristics as in nature. Isolated DNA has been manipulated chemically so as to produce a molecule that is markedly different from that which exists in the body. The Federal Circuit correctly concluded that in

Myriad the composition claims cover molecules that "have a distinctive chemical identity and nature" and therefore are "markedly different" from molecules that exist in nature. *Myriad* at 1351.

The Federal Circuit's decision was also made in accordance with the longstanding practice of the PTO (see PTO's 2001 Revised Utility Examination Guidelines for Gene Patent Application). The PTO has issued thousands of patents directed to DNA molecules for almost thirty years. *Myriad* at 1355. This Court stated in *Mayo* that changes in this longstanding practice of protecting DNA inventions under the broad scope of 35 U.S.C. § 101 should come from Congress, not the Courts. *Mayo* at 1304.

According to this Court, the drug-dosage calibration method used in *Mayo* merely and simply describes unpatentable natural laws, namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm. This Court found that the several steps in the process involve well-understood, routine, conventional activity previously engaged in by researchers in the field. The Court further stated that while it takes human action (the administration of a thiopurine drug) to trigger a manifestation of this relationship in a particular person, the relationship itself exists in principle apart from any human action. This Court concludes that the relation is a consequence of the way in which thiopurine compounds are metabolized by the body in an entirely natural process and that, therefore, a patent that simply describes that relation sets forth a natural law.

Regardless of whether one agrees with these findings of this Court or not, and even if this Court finds *Mayo* to be applicable to *Myriad*, these findings do not render Myriad's composition claim patent ineligible.

When an advance in science occurs and it relates to creating a new product that product is intended to be protected by our patent laws. And Courts should not concern themselves with the nuances of the chosen language under the admirably broad 35 U.S.C. § 101 to deny that protection. That is the evil of all these new § 101 arguments that this Court must put to rest. The filter of § 101 arguments was designed to be very large and not intended to be cluttered by semi-ingenuous lawyer created (and judicial) confusions. This broad filter created intentionally by Congress must not be narrowed by those more directed by monied interests than the inventions that move our country in the forefront of medical discoveries.

CONCLUSION

For the foregoing reasons, FICPI submits that in the present case human genes, isolated and created for the purpose of fighting cancer, should be found patent-eligible. Moreover, FICPI submits that this Court's *Mayo* decision has no bearing on this case.

Dated: January 24, 2013

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In The

Supreme Court of the United States

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ASSOCIATION FOR MOLECULAR
PATHOLOGY, et al.,

Petitioners,

v.

MYRIAD GENETICS, INC., et al.,

Respondents.

◆

**On Writ Of Certiorari To The
United States Court Of Appeals
For The Federal Circuit**

◆

BRIEF OF FIFTEEN LAW PROFESSORS AS *AMICI CURIAE* IN SUPPORT OF PETITIONERS

◆

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INTERESTS OF *AMICI CURIAE*

This brief is filed on behalf of the undersigned Law Professors identified in the Appendix.[1]

Law Professors teach and write about patents, intellectual property, and constitutional law. Law Professors are concerned that the Court should clearly state the requirements for an eligible invention modifying or applying a natural discovery. These are that: (1) the claim must be for a *creative* "inventive concept" that is *not analogous* to (is *markedly different* from) the natural discovery's structure and functions; and (2) the ineligible discovery must be treated *as if it were prior art* when evaluating whether such an inventive concept exists. Given this standard, Law Professors are concerned that thousands of claimed DNA molecules based on discovered gene sequences – including those at issue – have never been patent eligible inventions but have been issued as patents that have chilled scientific and medical innovation. This Court should clarify the standard for eligibility to avoid needless and costly litigation and foregone innovation.

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[1] The Petitioners' letter of consent for amicus briefs is on file with the Court; the Respondents' emailed consent accompanies this brief. This brief was not authored in whole or in part by counsel for any party. No one other than *Amici* and their counsel made a monetary contribution to preparing or submitting this brief.

SUMMARY OF THE ARGUMENT

In *Mayo Collaborative Services v. Prometheus Laboratories*, this Court reiterated that to be a patent eligible invention under Section 101 of the Patent Act, a claimed application of a natural discovery must reflect an "'inventive concept.'" In the 1952 Act, Congress restored for process claims this Court's "non-analogous" structure and function standard from *Ansonia Brass & Copper Co. v. Electric Supply Co.* When doing so, Congress also codified the corresponding "markedly different" standard for modified products of nature, later applied in *Diamond v. Chakrabarty*. The non-analogous structure and function standard properly distinguishes eligible from ineligible applications or modifications of natural discoveries. The standard has a long history dating to the 1793 Patent Act. To avoid further confusion, this Court should clarify its dicta suggesting that merely avoiding preemption or that artificial, human creation alone is sufficient for eligibility. The Court also should clarify that the presence or absence of a non-analogous inventive concept must be determined using a two-way test of the significance of the differences from the ineligible discovery and the other claim limits.

As this Court reiterated in *Bilski v. Kappos* and recognized in *Mayo*, Section 101 codified the rule adopted by this Court in *O'Reilly v. Morse* that treats ineligible natural discoveries as prior art. This rule assures that the claim is properly evaluated to assess whether it reflects an *original* inventive concept. This

Court should state explicitly that such prior art treatment is a Constitutional requirement.

Given the prior art treatment of the discovered natural gene sequences and molecules, the claimed "isolated DNA" molecules at issue clearly are not "markedly different" and are not patent eligible. Structurally, they are at most analogous to natural DNA and mRNA. Isolating the claimed DNA molecules is not (and was not) a creative advance beyond the ineligible scientific discovery. Functionally, new medical and scientific uses of the claimed molecules rely upon analogous, natural processes of sequence binding and replication.

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ARGUMENT

I. The Court Should Clarify That An "Inventive Concept" Requires *Non-Analogous (Markedly Different) Creativity* In The Modification Or Application Of Natural Discoveries.

In *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289 (2012), this Court reiterated that to be a patent eligible *invention*, a claimed application of an ineligible natural discovery[2]

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[2] *See, e.g., Bilski v. Kappos,* 130 S.Ct. 3218, 3225 (2010) ("'laws of nature, physical phenomena, and abstract ideas'" are not patent-eligible inventions) (citations omitted). The exclusions for natural discoveries are not, in fact, "exceptions" to statutory

(Continued on following page)

must reflect an "'inventive concept.'" *Id.* at 1294 (quoting *Parker v. Flook*, 437 U.S. 584, 594 (1978)). The very concept of "invention" requires a *creative*, human advance on prior knowledge or pre-existing nature. *See, e.g.*, 1 William C. Robinson, The Law of Patents for Useful Inventions, §§ 77, 78, at 116-17 (Little, Brown 1890) ("*The application of an idea*, not original with the person who applies it, *is not an invention*. . . . The mental faculties involved in the inventive act are the *creative* not the *imitative* faculties. . . . *[S]kill in applying [others' ideas] to practical results; none of these are creation*. . . .) (first and last emphasis added).

Once a discovery of a law of nature has been made, an inventive concept (a creative advance) can occur (if at all) only *in the application* of such a discovery. *See Mayo*, 132 S.Ct. at 1294 ("Still, as the Court has also made clear, to transform an unpatentable law of nature into a patent-eligible *application* of such a law, one must do more than simply state the law of nature while adding the words 'apply it.'"). Similarly, to be a patent eligible invention reflecting an inventive concept, a claimed product *modifying* a discovered product of nature must have "*markedly different* characteristics from any found in nature and . . . the potential for significant

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subject matter. *Id. See In re Alappat*, 33 F.3d 1526, 1553 n.13 (Fed. Cir. 1994) (en banc) (Archer, C.J., dissenting) ("Defining patentable subject matter is the *raison d'être* of § 101.").

utility." *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980) (emphasis added).

Although the Court has used different language to address processes applying scientific discoveries and products modifying natural material discoveries, it has always required that the "inventive concept" reflect more than the mere application of a discovery to a new "field of use," object, or purpose, and more than the "obvious" or "conventional," "token, post-solution" application or modification of a scientific principle or natural material. *See, e.g., Mayo*, 132 S.Ct. at 1301; *Bilski*, 130 S.Ct. at 3231. Novelty and utility of an application or modification alone have never been sufficient to establish an eligible, inventive concept. *See, e.g., Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130-31 (1948) (Bond "made an new and different composition of non-inhibitive strains which contributed utility and economy to the manufacture and distribution of commercial inoculants. But we think that that aggregation of species fell short of invention within the meaning of the patent statutes.").[3]

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[3] *See* 1 Robinson, *supra*, § 70, at 108 (Little, Brown 1890) ("[T]he novelty and utility of the result of the inventive act [are] *additional* conditions of patentability. The language of our courts might sometimes lead the incautious reader to imagine that the novelty and utility here required were to be taken as the *tests* by which the presence or the absence of the inventive act could always be determined. *Yet such is not the case.*") (emphasis added).

The Court, however, has not been sufficiently clear regarding what is meant by an "inventive concept." The Court in this case should provide the needed further guidance for lower courts, patent examiners, and the public. Such guidance will avoid unnecessary litigation and foregone sequential innovation resulting from improperly granting patents to purported inventions lacking an inventive concept. Such purported inventions add nothing to the "'storehouse of knowledge'" beyond what should be "'free to all men and reserved exclusively to none.'" *Bilski*, 130 S.Ct. at 3225 (quoting *Funk Bros.*, 333 U.S. at 130).

Specifically, the Court should clarify that an "inventive concept" requires a *creative*, *non-analogous* modification or application of an ineligible natural discovery. In other words, the inventive concept must possess a *markedly different* structure *and* function from the ineligible discovery. Otherwise, the claim to the purported invention will effectively protect the discovery itself, even if it does not claim all modifications and applications thereof. *See Mayo*, 132 S.Ct. at 1297 ("If a law of nature is not patentable, then neither is a process reciting a law of nature, unless that process has *additional features* that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself.") (emphasis added).

In 1952, Congress codified in Section 101 this Court's non-analogous structure and function (markedly different) standard for eligibility, which the

Court had long established as the means to avoid such monopolization. Without non-analogous creativity, natural discoveries could be monopolized in small bites (rather than swallowed whole) by claims to narrow but uncreative applications or modifications. The non-analogous structure and function standard also avoids the reductio ad absurdum that patents would never issue to claims applying or modifying natural discoveries. Rather, the standard assures that patents protect *only* the creative human contribution beyond what should be freely available.

Relatedly, the Court should clarify its dicta regarding concerns about "preemption," originating with *Gottschalk v. Benson*, 409 U.S. 63 (1972). *See id.* at 72 ("if the judgment below is affirmed, the patent would wholly pre-empt the mathematical formula and in practical effect would be a patent on the algorithm itself"). *See also, e.g., Mayo*, 132 S.Ct. at 1294; *Bilski*, 130 S.Ct. at 3230. These statements can be misconstrued to suggest that merely claiming a limited scope of application or modification of a natural discovery is sufficient for eligibility, even without an inventive concept. The Court also should clarify its dicta originating with *Chakrabarty*, which can be misconstrued to suggest that artificial, human creation alone is sufficient for eligibility. *See* 447 U.S. at 313 ("Congress thus recognized that the relevant distinction was not between living and inanimate things, but between products of nature, whether living or not, and human-made inventions."). *See also, e.g., J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 130 (2002). Non-preemption and artificiality are necessary but not sufficient conditions for eligibility. *See, e.g., Funk Bros.*, 333 U.S. at 130-31. Conversely, limiting eligibility to non-analogous applications or modifications of natural discoveries necessarily avoids preemption and assures artificial creation.

The Court also should clarify the method of assessing claims for the presence or absence of a non-analogous inventive concept. Because all inventions are essentially combinations of pre-existing elements, non-analogousness should be determined using a two-way test of the significance of the differences from both the underlying natural discovery and the other claim limitations. *See, e.g., KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418-19 (2007) ("inventions in most, if not all, instances rely upon building blocks . . . and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known."); *Intel Corp. v. U.S. Int'l Trade Comm'n*, 946 F.2d 821, 842 (Fed. Cir. 1991) ("'Virtually all inventions are combinations and virtually all are combinations of old elements.'") (citation omitted). The two-way test assures that the existence of an inventive concept will be properly assessed regardless of the form of the claim.

A. Section 101 Codified This Court's Precedents Requiring a Non-Analogous "Inventive Concept" for Eligibility.

In 1952, Congress made two significant changes to the requirements for patent eligible and patentable inventions. First, in the only directly relevant change to the law of patent eligibility, Congress overruled dicta from *In re Thuau*, 135 F.2d 344, 347 (C.C.P.A. 1943), which had been construed in later cases to suggest that *no* new *use* of an existing process or thing could constitute an eligible invention. *See, e.g.*, Pasquale J. Federico, *Commentary on the New Patent Act*, 75 J. Pat & Trademark Off. Soc'y 161, 177-78 (1993) (1954) (noting that *Thuau held* only that existing *compositions of matter* could not be considered new inventions and claimed as such simply because a new use for them had been found, "although some of the statements made in the decision are not completely defensible"). Congress did so by adopting in Section 100(b) of the new act a definition of "process," one of the four categories of patent eligible subject matter recited in Section 101 and its predecessors. That definition states that a statutory process "includes a new use of a known process, machine, manufacture, composition of matter, or material." 35 U.S.C. § 100(b).[4]

As the legislative history of Section 100(b) noted, moreover, "[t]he definition of process has been added

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[4] To simplify drafting, Congress also provided a definition of invention that includes inventions and discoveries. *See* 35 U.S.C. §§ 100(a), 101. Congress did not thereby intend to alter long-standing eligibility standards. Inclusion of the word "discovery" in the definition does not merit any significance, as the "invented or discovered" language has been in the Patent Act since its inception. *See* Patent Act of 1790, ch. 7, § 1 Stat. 109 (Apr. 10, 1790).

. . . to clarify the present law as to the patentability *of certain types* of *processes or methods* as to which some insubstantial doubts have been expressed." H.R. Rep. No. 82-1923, at 6 (emphasis added). This change was understood at the time to have been *limited to restoring* the Supreme Court's standard for the eligibility of *process* claims for new uses under the 1870 Act, which the lower courts had wrongly limited. Specifically, Congress intended to restore the *non-analogous use* standard this Court had articulated in *Ansonia Brass & Copper Co. v. Electric Supply Co.*, 144 U.S. 11 (1892). *See, e.g.*, Stefan A. Reisenfeld, *The New United States Patent Act in the Light of Comparative Law I*, 102 U. Penn. L. Rev. 291, 299-300 (1954) ("[T]he background of the amendment gives reason to assume that a newly discovered use for a known substance, machine or process is still only patentable *if it is not merely analogous or cognate to the uses heretofore made....* [I]n essence the new statutory definition of 'process' restores the broad principles of patentability flowing from a careful analysis of the exposition given by the Supreme Court in the *Ansonia* case.") (emphasis added). This was confirmed in *Application of Ducci*, 225 F.2d 683, 688 (C.C. P.A. 1955).

Ansonia Brass had held that "nothing is better settled in this court than that the application of an old process to a *new and analogous purpose does not involve invention*, even if the new result had not before been contemplated." *Id.* at 18 (emphasis added). *See* George T. Curtis, A Treatise on the Law of Patents for Useful Inventions in the United States of

America § 87, at 120 (Little Brown 2d ed. 1854) ("the new occasion or purpose . . . [must] not be merely analogous to the former occasions or purposes"). As discussed below, the Court's non-analogous structure and function standard for determining if an invention exists (and the corresponding "markedly different" standard for products modifying natural phenomena) dates to cases decided under the 1793 Act. Given the long history of that eligibility standard and the contemporaneous understanding to restore it, Section 100(b) should be understood to have codified the non-analogous use standard for *process* claims. *See* H.R. Rep. No. 82-1923, at 1 ("[T]he purpose of the bill is to revise and codify the laws relating to patents. . . ."). To hold otherwise would attribute to the 1952 Congress an intent to repeal centuries of settled doctrine without *any* discussion thereof.

Section 100(b), moreover, has no application whatsoever to *product* claims (machines, manufactures, and compositions of matter). Had Congress in 1952 intended *any* change to the standard for eligibility of products, Congress could have and would have said so (as it did for processes in Section 100(b)). Accordingly, the 1952 Act codified the Court's consistent, earlier interpretations of the relevant requirements for eligibility of products. *See, e.g., Central Bank of Denver v. First Interstate Bank of Denver*, 511 U.S. 164, 185 (1994); *Lorillard v. Pons*, 434 U.S. 575, 580 (1978).

The second, and indirectly relevant, change adopted by Congress in 1952 was to create a new *patentability* standard to address the degree of creative advance required for *eligible inventions*. Congress created a separate section (Section 103) with new language (obviousness) to determine whether the degree of creative advance reflected by an invention warranted granting a patent. In enacting Section 103, Congress was responding to the uncertainty that had been created regarding the degree of creativity required after *Cuno Engineering Corp. v. Automatic Devices Corp.*, 314 U.S. 84 (1941). *See* Federico, *supra*, at 183-84. *See also Graham v. John Deere Co.*, 383 U.S. 1, 14-17 (1966) (holding that Congress did *not* change the required degree of creativity when adopting Section 103).

Section 103, however, applies only to *inventions* that are determined to be eligible under Section 101. *See* 35 U.S.C. § 103(a) (2006) ("A patent may not be obtained though *the invention* is not identically disclosed or described as set forth in Section 102") (emphasis added); 35 U.S.C. § 102 (2006). Nothing in Section 103 changed the law regarding what qualifies as an invention in the first instance. *But cf.* Giles S. Rich, *Laying the Ghost of the "Invention" Requirement*, 1 APLA Q.J. 26, 29 (1972-73) ("[F]or the century following *Hotchkiss v. Greenwood*[, 52 U.S. (11 How.) 248 (1851),] we had what was called the 'requirement for invention,' which, I emphasize, we have *not* had for the past twenty years. Instead we have § 103.").

In particular, Congress when adopting Section 103 did not change the eligibility requirements in Section 101 *for claims that modify or apply ineligible discoveries of nature*. As this Court recognized in

Mayo (and as discussed in Section II below), natural discoveries are to be treated as if they were prior art against the applicant when determining if an invention has been made. However, nothing in Section 102 or in Section 103 treats natural discoveries as if they were prior art, or even excludes them from being patented. *See Mayo*, 132 S.Ct. at 1304 ("But §§ 102 and 103 say nothing about treating laws of nature as if they were part of the prior art when applying those sections."). The requirement for prior art treatment of natural discoveries, and thus their ineligibility and the need for an inventive concept in applying or modifying them, remains exclusive to Section 101. For this reason, Section 101 both is critically important and does not duplicate the obviousness standard of Section 103. *See generally* Joshua D. Sarnoff, *Patent Eligible Inventions After* Bilski: *History and Theory*, 63 Hastings L.J. 53, 56-58, 101-10 (2011).

B. The Non-Analogous (Markedly Different) Structure and Function Standard for Determining "Invention" Has Existed Since the 1793 Act.

The non-analogousness standard adopted by the Court in *Ansonia Brass* had a long history, for both products and processes. *See, e.g.*, Sarnoff, *supra*, at 63-84. In the 1793 Act, Congress confirmed the approach adopted by the Patent Board under the 1790 Act, excluding from a patent-eligible "discovery" a "simpl[e] chang[e to the] form or proportions" of machines or compositions of matter. Patent Act of 1793, ch. 11, § 2, 1 Stat. 318, 321 (Feb. 21, 1793). Under that Act, lower courts first confirmed for American law the exclusion of natural discoveries from the patent system. *See, e.g.*, *Lowell v. Lewis*, 15 F. Cas. 1018, 1019 (C.C. D. Mass. 1817) (No. 8,568) ("It has been often decided, that a patent cannot be legally obtained for a mere philosophical[5] or abstract theory."). *Cf. Boulton v. Bull*, 126 Eng. Rep. 651, 667 (1795) (Lord Eyre, C.J.) (no patents for "mere principle[s]"); *id.* at 663 (Buller, J.) (no patents for "an idea or principle alone"). The lower courts then confirmed that an eligible invention required the creation of a *non-analogous* thing or method (although the existence of an invention was sometimes conflated with the question of its novelty).[6] *See, e.g.*, *Whitney v. Emmitt*, 29 F. Cas. 1074, 1078 (C.C. E.D. Pa. 1831) (No. 17,585) ("if the patent is for [a new manufacture], it must be for something *substantially* new, different from what was before known; if [for a new manner of producing an old manufacture], the mode of operation must be *different*, not a *mere* change of the form and proportions; if both are the same in principle, structure, mode of operation, and produce the same result, they are not new, *though there may*

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[5] "Philosophical" was then understood to mean pertaining to the natural sciences. *See, e.g.*, The Compact Edition of the Oxford English Dictionary 180 (Oxford Univ. Press 1971).

[6] *See generally* Edward C. Walterscheid, *Novelty and the* Hotchkiss *Standard*, 20 Fed. Cir. B.J. 219, 227-28 (2010) (discussing "substantial novelty" and citing cases).

be a variance in some small matter for the purpose of evasion") (emphasis added).

In the 1836 Patent Act, Congress removed the statutory language regarding changes to form and proportions. *See* Patent Act of 1836, ch. 357, § 6, 5 Stat. 117, 119 (July 4, 1836). Nevertheless, under that Act, this Court reconfirmed in *Le Roy v. Tatham*, 55 U.S. (14 How.) 156 (1853), that natural discoveries are excluded from patent eligibility. *See id.* at 175 ("no one can claim in . . . [principles in the abstract] an exclusive right."). The Court then explained in *O'Reilly v. Morse*, 56 U.S. (15 How.) 62 (1854) – relying on the English precedent of *Nielson v. Harford*, 151 Eng. Rep. 1266 (1841) – that such natural discoveries are to be treated as *if they were prior art* (not as inventions of their discoverers) when evaluating the existence (or not) of an invention. *See* 56 U.S. (15 How.) at 116 (in *Nielson* "it was finally decided that this [discovered] principle [of physical science that hot air will promote fuel ignition better than cold] *must be regarded as well known*, and that the plaintiff had invented a mechanical mode of applying it to furnaces . . . [T]he court emphatically denied this [argued] right to such a patent [for the natural discovery itself].") (emphasis added). Finally, this Court and lower courts continued to require non-analogous new things or new uses for an invention to exist. *See, e.g.*, *Le Roy*, 55 U.S. at 175, 177 ("the invention is not in discovering the[elements of the power], but in applying them to useful objects. . . . 'If it is old and well known, *and applied only to a new purpose*, that does not make it patentable.'") (quoting *Bean v. Smallwood*, 2 F. Cas. 1142 (C.C. D. Mass. 1843) (No. 1,173)) (emphasis added); *Howe v. Abbott*, 12 F. Cas. 656, 658 (C.C. D. Mass. 1842) (No. 6,766) ("The application of an old process to manufacture an article, *to which it had never before been applied*, *is not* a patentable *invention*.") (emphasis added).

In the 1870 Act, Congress did not make any relevant change to the eligibility requirements, preserving the Court's interpretations of the limits of an eligible "invention." *See* Patent Act of 1870, ch. 230, § 24, 16 Stat. 200 (July 8, 1870). Shortly before *Ansonia Brass*, the Court reiterated in *The Telephone Cases* that more than mere application of a natural discovery to a new use was required for eligibility. *See Dolbear v. American Bell Telephone Co.*, 126 U.S. 1, 534 (1888) ("In the present case the claim is not for the use of a current of electricity in its natural state as it comes from the battery . . . but for putting a continuous current, in a closed circuit, into a certain specified condition. . . ."). Similarly, as stated by the Court of Appeals in *Wall v. Leck*, 66 F. 552 (9th Cir. 1895):

> [E]mployment of [a scientific discovery] in the modes or through the instrumentalities by which it is applied in nature is a mere limitation of what every man is able to perceive and reproduce as well as [t]he [patentee]. All endeavors to confine it to himself are at once futile and unjust. . . . Not until some new instrument or method is contrived for its

> direction *towards ends which it cannot naturally accomplish* does his creative genius manifest itself.

Id. at 558 (citing 1 Robinson, *supra*, § 136) (emphasis added).

Although this Court when addressing modified products of nature ("natural phenomena" or "physical phenomena"[7]) used different terminology, it also required for invention a non-analogous structure and function. For example, in *Hartranft v. Wiegmann*, 121 U.S. 609 (1887), the Court held that to qualify as a manufacture required "a new and different article, having a *distinctive* name, character, or use. . . . The application of labor to an article, either by hand or by mechanism, does not make the article necessarily a manufactured article. . . ." *Id.* at 615. Similarly, in *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1 (1931), the Court addressed a novel and useful (but structurally and functionally analogous) borax-treated preserved fruit. The Court held that for invention to exist "a new *and different* article must emerge." *Id.* at 13 (emphasis added). Given the known preservative functions of borax and the food function of fruit, making the novel and useful structural combination was not an invention. *See id.* at 14.

As the Commissioner of the Patent Office (and one of the principal drafters of the 1952 Patent Act) recognized shortly after *American Fruit Growers*, some patents had been improperly issued under the 1870 Act (such as Pasteur's yeast patent) for isolated or purified natural products that lacked the requisite marked differences of structure and function. *See* Pasquale J. Federico, *Louis Pasteur's Patents*, 86 Science 327 (October 8, 1937) ("A claim of this type would now probably be refused by the examiner, since it may now be doubted that the subject-matter is capable of being patented.").[8]

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[7] *See, e.g., Mayo,* 132 S.Ct. at 1293 (citations omitted); *Bilski,* 130 S.Ct. at 3225 (citations omitted).

Just prior to the 1952 Act, moreover, this Court reaffirmed that invention required a creative, non-analogous inventive concept, not merely novelty and utility. The bacterial cultures at issue in *Funk Brothers* were both structurally novel (as they had not previously been combined) and had valuable new uses (because of the natural discovery of the non-inhibition property of the strains). Nevertheless, the Court held the combination to lack the required inventive concept beyond merely applying the new discovery. *See Funk Bros.*, 333 U.S. at 131 ("The aggregation of select strains of the several species into one product is an application of that newly-discovered natural principle. But however ingenious the [scientific] discovery of that natural principle may have been, *the application of it is hardly more than an advance in the packaging* of the inoculants.") (emphasis added). *Cf. Mackay Radio & Tel. Co. v. Radio Corp. of Am.*, 306 U.S. 86, 94 (1939) ("We assume, without deciding the point, that this advance was *invention* even though it was achieved by the logical application of a known scientific law to a familiar type of antenna.") (emphasis added).

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[8] The comparison to the instant case is apt, although the magnitude of the granting errors is much greater in regard to gene patents. Further, isolated and purified natural products may become eligible *if* they have become non-analogous things. *Cf. Parke-Davis & Co. v. H. K. Mulford Co.*, 189 F. 95, 103 (S.D.N.Y. 1911) (finding isolated and purified adrenaline to be a change of kind rather than of degree from the natural substance, but adopting unfortunate dicta that "even if it were merely an extracted product without change, there is no rule that such products are not patentable"), *aff'd in part, rev'd in part*, 196 F. 496 (2d Cir. 1912)); Jon M. Harkness, *Dicta on Adrenalin(e): Myriad Problems With Learned Hand's Product of Nature Pronouncements in* Parke-Davis v. Mulford, 93 J. Pat. & Trademark Off. Soc'y 363, 389-92 (2011) (noting Judge Hand's lack of attention to the product of nature issue given the case focus on novelty).

C. The Court Should Clarify Its Dicta Suggesting that Merely Avoiding Preemption or Artificial, Human Creation Is Sufficient for Eligibility.

As the Court recently noted in *Mayo*, its precedents establish three concerns. First, eligibility requires a claimed process applying a natural law to reflect an inventive concept that "in practice amounts to significantly more than a patent on the natural law itself." 132 S.Ct. at 1294 (citations omitted). Second, eligibility should not "'depend simply on the draftsman's art' without reference to the 'principles underlying the prohibition against patents for [natural laws].'" *Id.* (citation omitted). Third, courts should not "uphold[ ] patents that claim processes that too broadly preempt the use of a natural law." *Id.* The first concern is met by the non-analogous (markedly different) structure and function standard. The second concern is met by proper implementation of that standard, which requires both prior art treatment of ineligible discoveries and a two-way test of the significance of the differences from the prior art (as discussed below). However, the Court's third concern can lead to significant confusion.

The lack of *inventive creativity* and scope of *preemption* are entirely different concerns, and only the former is relevant for eligibility determinations. *See, e.g.*, Katherine J. Strandburg, *Much Ado About Preemption*, 50 Hous. L. Rev. 563, 564-67 (2012) (discussing use of "preemption" as a measure of the effects of claims on downstream innovation; noting that most of the Court's eligibility decisions turn not on overbreadth but on whether the "application of per se unpatentable elements is sufficiently inventive to traverse the boundary between unpatentable and patentable terrain"). The Court's dicta, unfortunately, have sometimes conflated these two concerns. *See, e.g., Mayo*, 132 S.Ct. at 1301 ("the claim [in *Benson*] (like the claims before us) was overly broad; it did not differ significantly from a claim that just said 'apply the algorithm.'").

The Court thus should clarify that its concern about preemption of innovation *is not a test for* *determining eligibility* of claims applying or modifying ineligible natural discoveries. Rather, preemption was one of the historical motivating reasons for finding natural discoveries *to be ineligible in the first instance*. *See* Sarnoff, *supra*, at 85-90 (tracing religious concerns over patenting "God's work" that corresponded with utilitarian views that private ownership of natural discoveries would be bad innovation policy). As this Court held in *The Telephone Cases*, *if* an eligible, inventive concept is present in a claim applying a natural discovery, *then* the claim can preempt the entire scope of application of that concept (not of the discovery).[9] *See Dolbear*, 126 U.S. at 534-35 ("It may be that . . . practically, [Bell's] patent gives him its exclusive use for [transmitting speech by electricity], but that does not make his claim one for the use of electricity distinct from the particular process. . . . It will, if true, show more clearly the great importance of his [creative human] discovery, but it will not invalidate his patent."). A creative invention, just like a law of nature, may be either broad or narrow; a claim to the former may preempt its full scope, while a claim to the latter is simply ineligible. *Cf. Mayo*, 132 S.Ct. at 1303.[10]

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[9] *See, e.g.*, 1 Robinson, *supra*, § 81, at 124 & n.3 ("The law regards him as the owner of the invention for any and every purpose to which it can be applied, and thus secures to him the entire benefit of his original idea. . . . [This] doctrine is, therefore, limited to such benefits *as the inventive skill of the inventor in question has actually conferred upon the public*. . . .") (emphasis added). The scope of application of *inventions* is currently limited only by the reverse doctrine of equivalents. *See Westinghouse v. Boyden Power Brake Co.*, 170 U.S. 537, 571, 573 (1898).

The Court's dicta, moreover, can easily be misconstrued to suggest that merely avoiding preemption of a natural discovery is sufficient for eligibility. For example, if avoiding preemption of all uses of Einstein's discovery were sufficient for eligibility, the hypothetical claim discussed in *Mayo should* be eligible. *See* 132 S.Ct. at 1297 (instructing linear accelerators to refer to Einstein's mass-energy conversion law to determine "how much energy an amount of mass has produced (or vice-versa)."). That is because use in linear accelerators to determine mass-energy conversions would be only one, very small subset of applications of Einstein's law, employing a specific, complex machine to achieve a new, particular, and valuable use.[11] Rather, the reason such a claim is ineligible is that the use claimed is directly analogous to the natural discovery, and thus there is no creative inventive concept in that application.

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[10] To the extent the Court remains concerned over the effects on downstream innovation of granting broad patents for eligible inventions, it may wish to revisit in an appropriate case the recent radical restriction of the scope of the experimental use "exception" to infringement. *See, e.g., Roche Prods. Inc. v. Bolar Pharms.*, 733 F.2d 858 (Fed. Cir. 1984); *Madey v. Duke Univ.*, 307 F.3d 1351 (Fed. Cir. 2002). *Cf. Proveris Scientific Corp v. InnovaSystems, Inc.*, 536 F.3d 1256 (Fed. Cir. 2008). Historically, that doctrine prevented research on *and with* patented inventions from being considered infringing acts, permitting unrestricted, further discovery, invention, and innovation. *See generally* Henrik Holzapfel & Joshua D. Sarnoff, *A Cross-Atlantic Dialog on Experimental Use and Research Tools*, 48 IDEA 123, 133-44 (2008) (discussing the history of the doctrine).

Similarly, the ineligible claim actually at issue in *Mayo* would not have become eligible simply by avoiding preemption of all (or most) uses of the discovered correlation. For example, it would add no creativity to limit the claim to the conventional treatment step of actually adjusting the dose of the synthetic drugs administered, but the claim may routinely be practiced without that added step (*e.g.*, in diagnosis, for further study, etc.). *Cf. id.* at 1298 ("the combination amounts to nothing significantly more than an instruction to doctors to apply the applicable laws when treating their patients."). *But cf. id.* at 1303 ("the patent claims do not confine their reach to particular applications of those laws.").

Clarifying that preemption is not directly relevant to determining eligibility will discourage claim drafting efforts seeking to limit the scope of application of natural discoveries without adding creativity, in an effort to evade this Court's historic limits on eligibility codified by Section 101. *Cf. Mayo*, 132 S.Ct. at 1297 ("the 'prohibition against patenting abstract ideas "cannot be circumvented by attempting to limit the use of the formula to a particular technological environment."'") (citations omitted); *id.* at 1300 ("'"*Flook* established that . . . adding token post-solution components did not make the concept patentable."'") (citations omitted). It will thereby also avoid unnecessary litigation over patents that lack an inventive concept but monopolize only some, not all, of the ineligible discovery itself.

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[11] The example demonstrates that this Court properly rejected the "machine-or-transformation" approach as a *test* of eligibility in *Bilski*. *See* 130 S.Ct. at 3226-27.

Similarly, this Court should clarify that its dicta distinguishing artificial, human creations from discovered products of nature state a necessary but not a sufficient condition for eligibility. *See Chakrabarty*, 447 U.S. at 313 ("human-made inventions."). Again, this dicta could readily be misconstrued to suggest that mere artificial, human applications or modifications of natural discoveries are eligible. Were mere artificiality sufficient, many of this Court's precedents could not be justified. For example, in *Mayo*, the thiopurine drugs administered as part of the claims were synthetic human creations, and as the Court noted "[w]hile it takes a human action (the administration of a thiopurine drug) to trigger a manifestation of this relation in a particular person, the relation itself exists in principle apart from any human action." 132 S.Ct. at 1297. The treated fruit in *American Fruit Growers* and the combined bacterial strains in *Funk Brothers* were artificial, human creations. So was synthetic alizarine, which the Court expressly held in *Cochrane v. Badische Analin & Soda Fabrik*, 111 U.S. 293 (1884), was not an eligible invention merely because claimed as an artificial preparation. *See id.* at 311 ("Calling it artificial alizarine did not make it a new composition of matter, and patentable as such, by reason of its having been prepared artificially") (citing *American Wood Paper Co. v. The Fibre Disintegrating Co.*, 90 U.S. (23 Wall.) 566, 593 (1874)).

The Court thus should clarify that inventions must not only be "human-made," but also markedly different from natural products. As with clarifying preemption dicta, the Court will help to avoid further improper patent grants, further efforts to evade eligibility limits, and further unnecessary litigation.

D. The Court Should Adopt a Two-Way Test of the Significance of the Differences from the Natural Discovery.

Although this Court's dicta have sometimes conflated the questions of whether an inventive concept is present and whether preemption exists, the Court has properly looked for an inventive concept from both perspectives of the claimed combinations: how do the additional elements of the claim creatively apply or modify an ineligible natural discovery; and what does the discovery add to an existing product or process. For example, as the Court discussed in *Mayo*, *Flook* involved an ineligible claim combining an ineligible mathematical equation (treated as if it were prior art) with a known process for catalytic conversion of hydrocarbons. *See* 132 S.Ct. at 1299. The Court in *Flook* sought to determine eligibility *first* by noting that the claim did not provide any guidance regarding how the elements of the process worked with the ineligible formula (and thus “did not limit the claim to a particular application” of the discovery), and *second* by analyzing the nature of the process limitations added to the ineligible formula (which were “‘well known’ to the point where, putting the formula to the side, there was no ‘inventive concept’”). *Id.* (*quoting Flook*, 437 U.S. at 594).

This two-way analysis of non-analogousness is the proper approach. The structures and functions *identified in nature* may not by themselves suggest combination with an existing process or product, but that process or product may itself suggest the combination when the natural discovery is similar to existing structures and functions already employed. For example, the Pythagorean theorem by itself may not have been applied in architecture prior to its discovery, and thus its discovery may not have suggested combination with rulers and compasses to make diagrams. But given prior calculations to make diagrams, substituting the theorem (once discovered and treated as prior art) would have been directly analogous (even if novel and highly useful) to existing architectural processes. No inventive concept would exist in claiming the theorem’s use for this purpose.

Similarly, as this Court also discussed in *Mayo*, the claimed process in *Diamond v. Diehr*, 450 U.S. 175 (1981), was found eligible

> because *of the way the additional steps of the process integrated the equation into the process as a whole*. . . . [The Court] nowhere suggested that all these steps, or at least the combination of those steps, were in context obvious, already in use, or purely conventional. . . . These other steps *apparently added to the formula something that* in terms of patent law's objectives *had significance* – they transformed the process into an inventive application of the formula.

132 S.Ct. at 1298-99 (emphasis added).[12] Again, the Court applied a two-way analysis for a non-analogous inventive concept: adding the discovery to something and the other way around. One-way non-analogousness is not enough.

The two-way test for an inventive concept makes eminent sense, given prior-art treatment of ineligible discoveries. Either the discoveries or the elements they are combined with may suggest making a claimed combination (as may extrinsic motivations, alternative problems, or ordinary human practices). *See, e.g., KSR Int'l*, 550 U.S. at 418-22. The two-way analysis, moreover, should make it easier to determine the presence or absence of an inventive concept regardless of the form of the claim as a process or as a product (machine or system, manufacture, or composition of matter). In all cases, the question will be what the functional or structural claim limits *creatively* add to the natural discovery and what the ineligible discovery *creatively* adds to prior art processes or things. So long as the two-way test of non-analogousness is employed, the Court can leave for further judicial and administrative development the requisite *degree* of creative advance that will establish non-analogousness in particular cases.

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[12] This holding, however, was highly questionable given that similar rubber curing processes not continuously monitoring temperature, but using the same equation, had been in use. *See* 450 U.S. at 179. The Court would assist understanding and avoid untold future litigation if it simply acknowledged here that *Diehr* was wrongly decided.

II. The Court Should Reaffirm That Ineligible Discoveries Must Be Treated As Prior Art When Evaluating The Presence Or Absence Of An Inventive Concept.

In *Bilski*, the Court reiterated language originating in *O'Reilly* that natural discoveries must be treated as if they were prior art for eligibility. "The Court concluded [in *Flook*] that the process at issue there was 'unpatentable under § 101, not because it contain[ed] a mathematical algorithm as one component, but because once that algorithm [wa]s *assumed to be within the prior art*, the application, considered as a whole, contain[ed] no patentable *invention*.'" *Id.* at 3230 (quoting *Flook*, 437 U.S. at 594) (emphasis added). *See Flook*, 437 U.S. at 595 ("If we assume that that method was also known, as we must under the reasoning in *Morse*"); *O'Reilly*, 56 U.S. (15 How.) at 115-16. The Court, however, has failed to emphasize the significance of prior art treatment or to explain why it is needed for determining whether an inventive concept exists. It should do so here.

A. Without Prior Art Treatment, Any Claimed Modification or Application of an Ineligible Discovery Can Masquerade As an Inventive Concept.

Although "the discovery of . . . a [natural] phenomenon cannot support a patent," it is prior art treatment of ineligible discoveries that mandates that "there [be] some *other inventive concept* in [their] application." *Flook*, 347 U.S. at 594 (emphasis added). This is true even when considering a claimed invention "as a whole." *Id.* Otherwise, the creative advance of the discovery itself may be improperly viewed as the "inventive concept" of any claim that modifies or applies it. *See, e.g., Diehr*, 450 U.S. at 192 ("To hold otherwise would allow a competent draftsman to evade the recognized limitations on the type of subject matter eligible. . . ."); *Alappat*, 33 F.3d at 1554 (Archer, C.J., dissenting) ("The discovery of music does not become patentable subject matter simply because there is an arbitrary claim to some structure."). This is because it may take creativity to *discover* the ineligible product of nature or scientific principle but not to *combine* it (once known) with the existing art.

For example, without prior art treatment, substituting a new algorithm for analogous timing calculations in a hydrocarbon cracking process might appear to be an inventive concept, even if the only creative advance were in the ineligible algorithm. Conversely, adding the cracking process to the algorithm might appear to be a creative advance without prior art treatment, particularly if the algorithm was not discovered in (and thus did not suggest its use in) the context of cracking. By treating the ineligible discovery as prior art, both the algorithm and its properties will already be taken into account when assessing whether its substitution into an existing process is a creative, non-analogous advance.

B. The Court Should Explicitly Hold That Prior Art Treatment Is a Constitutional Requirement.

Prior art treatment of ineligible discoveries is no mere historical accident. Through the late 18th century, "invention" had a technical meaning that distinguished it from discoveries of scientific principles, natural phenomena, and fundamental information (as well as from discoveries of exploration or in the liberal and fine arts).[13] Science, nature, and abstract ideas were thought to originate from God. Accordingly, natural discoveries were not thought to be human creations that were the proper objects of exclusive private property rights.[14]

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[13] *See, e.g.,* Edward C. Walterscheid, The Nature of the Intellectual Property Clause: A Study in Historical Perspective 365-66, 375-76 (William S. Hein & Co. 2002) (hereinafter "Walterscheid, *Study*")); John R. Thomas, *The Patenting of the Liberal Professions,* 40 B.C. L. Rev. 1139, 1164-65 (1999).

Further, scientists who made such discoveries were thought to owe moral duties to share their discoveries freely with the public, which was then entitled to benefit from the information. As Lord Camden stated in 1774, scientists are "intrusted by Providence with the delegated power of imparting to their fellow-creatures that instruction which heaven meant for universal benefit; they must not be niggards to the world, or hoard up for themselves the common stock." 17 The Parliamentary History of England col. 999 (William Cobbett ed., 1806-20) (1774). This perceived moral duty of scientists – which corresponded with utilitarian beliefs of the social benefits of protecting the public domain – historically grounded the prior art treatment of natural discoveries.[15]

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[14] *See* Christine MacLeod, Inventing the Industrial Revolution: The English Patent System 1660-1800, at 198-203 (Cambridge Univ. Press 2002) (1988); Walterscheid, *Study, supra*, at 39, 375-76. *Cf. Feist Publ'ns, Inc. v. Rural Tele. Serv. Co.*, 499 U.S. 340, 347 (1991) (distinguishing "discovery" from "creation"; holding that facts cannot be original creations of their discoverers); Letter from Thomas Jefferson to Isaac MacPherson (Aug. 13, 1813), *in* Thomas Jefferson, The Portable Thomas Jefferson 525, at 529-30 (Merrill D. Peterson ed., Penguin Books 1977) (explaining why ideas are not subject to property rights).

[15] *See* 1 *Robinson, supra*, § 25, at 39 ("To benefit by the discoveries of his fellow-men is thus not only a natural right, it is also the natural duty which every man owes to himself and to society; and the mutual, universal progress thence resulting is the fulfillment of the earthly destiny of the human race."). *See generally* Sarnoff, *supra*, at 84-90.

Otherwise, as noted above, claims to uncreative applications would be able to partially monopolize natural discoveries. *Cf. Mayo*, 132 S.Ct. at 1293 ("monopolization of those [basic] tools [of scientific and technological work] through the grant of a patent might tend to impede innovation more than it would tend to promote it").

This history is reflected in the Constitution's language and purpose. As this Court has recognized, the Constitution requires *originality* for copyrights and patents, given authorization of exclusive rights only for "Authors and Inventors to their respective . . . Writings and Discoveries." U.S. Const., art. I, § 8, cl. 8.[16] An original "Discovery" of an "Inventor" in the constitutional sense requires *invention*, which in turn requires a *creative* human advance *beyond* any new natural discovery. *See, e.g., Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 476 (1974) ("discovery is something less than invention"); *In re Kemper*, 14 F. Cas. 286, 287 (C.C. D. D.C. 1841) (No. 7,687) ("A discovery, in this sense, is not the subject of a patent" but as used in the Constitution is always "synonymous with invention."); Rich, *supra*, at 29-34 (a qualitative

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[16] *See Feist Publ'ns, Inc. v. Rural Tel. Serv. Co.,* 499 U.S. 340, 346 (1991) ("Originality is a constitutional requirement. . . . [In *The Trade-Mark Cases,* t]he Court explained that originality requires independent creation *plus a modicum of creativity*. . . . [In *Burrow-Giles,*] the Court emphasized the *creative* component of originality.") (citing *In re Trade-Mark Cases,* 100 U.S. 82, 94 (1879), and *Burrow-Giles Lithographic Co. v. Sarony,* 111 U.S. 53, 58 (1884)) (emphasis added).

"invention" requirement is reflected in the Constitution's restriction to "Inventors"); Albert H. Walker, Text-book of the Patent Laws of the United States of America 2 (2d ed. 1889) ("The word 'discovery' . . . in the Constitution. . . . means invention . . . and . . . nothing else."). *Cf. Mazer v. Stein*, 347 U.S. 201, 220-21 (1954) (Douglas, J., concurring) ("Perhaps these are all 'writings' in the constitutional sense. But to me, at least, they are not obviously so. It is time that we came to the problem full face."). *See generally* Oskar Liivak, *The Forgotten Originality Requirement: A Constitutional Hurdle for Gene Patents*, 87 J. Pat. & Trademark Off. Soc'y 261, 273-75 (2005).

Without reflecting an inventive concept that goes beyond (is not analogous to) an ineligible discovery, a claimed product or process will lack originality under the Constitution. Prior art treatment assures that uncreative applications or modifications of natural discoveries are not considered original inventions. No matter how much effort or creativity may have gone into identifying natural discoveries, the discoveries themselves and analogous applications or modifications of them simply are not within the constitutional grant of power. *Cf. Morton v. New York Eye Infirmary*, 17 F. Cas. 879, 884 (C.C. S.D.N.Y. 1862) (No. 9,865) ("'A discovery may be brilliant and useful, and not patentable. . . . The new force or principle brought to light . . . can be patented *only* in connection *or combination* with the means by which, or the medium through which, it operates.'") (emphasis added).

The Court in this case should expressly hold that prior art treatment of ineligible discoveries is a constitutional requirement. Without such a clear statement of the Constitution's limits, foreseeable lobbying may induce Congress to seek to validate retroactively (to a decision in this case) the thousands of ineligible gene patents that have issued.

III. The Claimed Isolated DNA Molecules Are Ineligible, As Their Structure And Functions Are At Most Analogous To Natural DNA And mRNA.

Given prior art treatment of natural discoveries, the claims at issue for isolated DNA molecules (and thousands of other patents' claims for isolated and/or purified DNA) are clearly ineligible. The claimed molecules do not possess non-analogous (markedly different) structures or functions from the discovered, naturally occurring materials. For example, some of the claims at issue are drawn to "isolated DNA" molecules having a sequence "coding for a *BRCA*1 polypeptide" (a protein) or containing "at least 15 nucleotides" (DNA bases) of that sequence. U.S. Patent No. 5,747,282, cl. 1, 5. The discovered *BRCA*1 gene and its location on the chromosome, the discovered natural chromosomal DNA and mRNA molecules, and the discovered natural chromosomal DNA and corresponding mRNA sequences all must be treated as prior art when evaluating whether the claimed "isolated DNA" molecules are inventions. It should be immediately apparent – however the claims are construed – that the claimed isolated DNA molecules do not have *markedly different* (non-analogous) structures from the natural DNA and mRNA on which they are based.[17]

It is precisely the identity of the claimed molecules' sequences to those of the discovered DNA and corresponding mRNA that makes such isolated DNA useful and valuable. The sequence identity clearly makes the claimed DNA molecules structurally *analogous* to the discovered natural chromosomal DNA and corresponding mRNA. This is true even if the claim term "isolated DNA" is construed – beyond the words themselves – to require minor differences in chemical structure (such as methylation) from naturally occurring DNA.[18] Similarly, even if the claim term "isolated DNA" is construed to require synthetically created molecules,[19] it would not make the claimed molecules *markedly different*. As noted above in regard to *Cochrane*, artificial production alone is not sufficient for eligibility. This should be particularly true when artificial production merely reproduces the discovered natural molecules. *See, e.g.*, Liivak, *supra*, at 282-90.

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[17] All of the claimed fifteen-nucleotide DNA sequences will exist in chromosomal DNA without removing introns (although the chromosomal DNA sequences may not be "isolated" from the surrounding sequences). Similarly, the identified protein-coding sequences (with introns removed) will naturally exist in mRNA, which is not DNA but is subject to the genetic code.

[18] *See generally* J. Sambrook et al., Molecular Cloning: A Laboratory Manual (2d ed. 1989).

[19] Claims unlike those at issue here that are expressly limited to "cDNA" also will be ineligible, whether or not the term "cDNA" is construed to require synthetic production, precluding application to naturally occurring molecules.

In fact, the claimed "isolated DNA" molecules (even if synthetically produced) may be structurally *identical* to natural materials. Because of natural viral transcription, both protein-coding-sequence and 15-base-pair-sequence molecules *may* exist in nature separated from the chromosomal DNA material. Further, the claimed isolated DNA molecules may be identical even if chemically modified, given that chemical modification also *may* occur naturally (although statistically may not *always* occur in the same locations).[20]

It should also be apparent that "isolating" the specified DNA molecules is *not* a creative, non-analogous inventive concept. Once the gene's location and the chromosomal DNA and corresponding mRNA molecules and sequences have been identified, determined, and treated as prior art, isolating and synthetically producing the relevant DNA molecules is (and was at the relevant time) a wholly routine and conventional action.[21] The claimed DNA

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[20] *See, e.g.*, Yingying Zhang & Albert Jeltsch, *The Application of Next Generation Sequencing in DNA Methylation Analysis*, Genes 85, 86 (2010).

[21] *See, e.g.*, Sambrook, et al., *supra*. Further, both separation from chromosomes and synthetic production of the relevant sequences may occur in the very process of the scientific discovery

(Continued on following page)

molecules at issue thus are not like the claimed bacteria at issue in *Chakrabarty*, which reflected a non-analogous combination (at least at the time).[22]

Nor are the functions of the claimed, isolated DNA molecules markedly different from (not analogous to) those of the natural DNA on which they are based. The medical uses of the claimed isolated DNA molecules as diagnostics, and the scientific uses of them as probes or primers, depend upon and are directly analogous to the natural functions performed by chromosomal DNA and corresponding mRNA. These natural functions include the chemical and biological processes of homologous sequence binding and sequence replication.[23] These functions are not inventive concepts, even if they are novel and valuable analogous applications of the natural discoveries. These functions depend on the natural discoveries at

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of the gene sequence, demonstrating the lack of creative advance beyond the discovery. *See, e.g.*, Brief of Amicus Curiae Law Professor Christopher M. Holman in Support of Neither Party, *Association for Molecular Pathology v. U.S. Patent and Trademark Office*, 689 F.3d 1303 (Fed. Cir. 2012), at 6-7.

[22] In *Chakrabarty*, the Court focused on the question of whether Congress had prohibited claims to living organisms, not on the question of invention itself. *See* 447 U.S. at 310-18. Nevertheless, the Court distinguished the combination in *Funk Brothers* by noting the markedly different character of the combination at issue, and held its decision was consistent with *Flook*. *See id.* at 310, 315. The Court did not reach the eligibility of a claim to a more analogous, purified natural product, as the issue had been mooted. *See id.* at 306-07.

[23] *See generally* Sambrook, et al., *supra*.

least as much as the discovered mutual inhibition properties of the combined bacterial strains in *Funk Brothers* and the discovered food preserving function of borax and edible nature of fruit in *American Fruit Growers*.

◆

CONCLUSION

For the foregoing reasons, the Court should affirm the District Court's rejection of the patent claims at issue, adopt the non-analogous structure and function (marked differences) test of an inventive concept, and hold that prior art treatment of ineligible discoveries is a constitutional requirement.

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AMICUS CURIAE BRIEF

Supreme Court U.S.
FILED
2013
OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,
Petitioners,

v.

MYRIAD GENETICS, INC., ET AL.,
Respondents.

**On Writ of Certiorari to the
United States Court of Appeals
for the Federal Circuit**

BRIEF OF DRS. LARRY GEIER, WILLIAM HARB, ADAM OFER, AND DONALD APTEKAR AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

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INTERESTS OF *AMICI CURIAE*[1]

Amici are a group of practicing physicians whose primary obligation is to provide their patients with the best medical care possible. In this capacity, amici view BRCA1 and BRCA2 testing as vital tools that empower patients to better plan for their future medical needs and take preventative steps when necessary. Amici have worked with Myriad in the past to promote awareness of genetic testing, and their experiences with Myriad belie the notion that patenting human genes results in harm to human health. To the contrary, Myriad has directed substantial resources towards making BRCA testing widely available, and in doing so, has saved thousands of lives.

Dr. Larry J. Geier, M.D., is an oncologist and Assistant Professor at the University of Kansas Medical Center in Kansas City, KS. He is board-certified in Internal Medicine, Medical Oncology, and Hematology, and specializes in genetic risk assessment and the management of genetic cancers. As one of the leading oncologists in the country, Dr. Geier serves as a resource for other physicians nationwide and speaks at multiple conferences each year.

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[1] Pursuant to Rule 37.6, *amici* affirm that no counsel for a party authored this brief in whole or in part and that no person other than *amici* and their counsel made a monetary contribution to its preparation or submission. Petitioners' blanket letter of consent to the filing of amicus briefs has been filed with the Clerk's office. Respondents' consent to the filing of this brief is being filed with the Clerk's office together with the brief.

Dr. William Harb, M.D., is a colorectal surgeon based in Nashville, TN. He is board-certified in General Surgery and Colon and Rectal Surgery, and has a clinical focus on inherited colon cancer. In this capacity, Dr. Harb has kept at the forefront of genetic testing, and published numerous articles on colon and rectal surgery. As a colorectal surgeon in private practice, he has regularly utilized genetic testing for the betterment of his patients.

Dr. Adam Ofer, M.D., is the Director of Gynecology at the Norwalk Hospital in Norwalk, CT. He is board-certified in Obstetrics and Gynecology, with a special focus on preventative care, hereditary risk assessment, and minimally-invasive surgical techniques. Throughout his career, Dr. Ofer has embraced new technologies and procedures to better serve his patients.

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SUMMARY OF ARGUMENT

1. The briefs filed by petitioners and their amici assert that patenting human genes leads to a slew of

adverse consequences for human health and medical research. But the impact of Myriad Genetics' BRCA patents belies this notion. Numerous studies demonstrate that Myriad has benefited the field of medicine on multiple fronts. Myriad has raised awareness of BRCA testing among physicians and patients, and in turn, has helped thousands of individuals discover that they are vulnerable to breast and ovarian cancer and take preventative measures. In addition to bringing attention to BRCA testing, Myriad has successfully made its tests widely accessible. Working with healthcare providers and funding its own programs to provide testing to individuals in difficult economic circumstances, the company has made BRCA testing available to 95% of appropriate American patients. Finally, far from hindering cancer research, Myriad has played a key role in supporting both internal and third-party cancer research.

2. Amici's own personal experiences verify that Myriad's BRCA1 and BRCA2 patents have benefitted physicians and patients alike. Every day, practicing physicians rely on BRCA testing to counsel and treat patients at risk of developing breast and ovarian cancer. But only a decade ago, such testing was viewed as a controversial and "niche" diagnostic. Under Myriad, amici have witnessed BRCA testing blossom into a widely recognized, widely available medical tool. As a result of the company's awareness campaigns, more people than ever are being tested, and physicians are better able to serve their patients. Amici believe that Myriad's efforts to

responsibly use and license its patents confirm the wisdom of permitting genes to be patented.

3. Amici also adamantly disagree with the notion that patenting human genes is inherently unethical. A practicing physician's highest obligation is to her patients, and it is beyond dispute that Myriad has helped nearly one million patients better plan for their future medical needs by providing BRCA testing. In this regard, Myriad's efforts have been ethically laudable, and easily outweigh concerns about hindering future research.

ARGUMENT

I. MYRIAD'S EFFORTS TO MAKE BRCA TESTING WIDELY ACCESSIBLE AND PROMOTE CANCER RESEARCH DEMONSTRATE THE SALUTARY EFECTS OF PATENTING GENETIC MATERIAL.

The briefs filed by petitioner and the American Medical Association (AMA), among others, urge that patenting genetic material impedes the quality of health care and stymies medical research. *See, e.g.*, Pet. Br. 56-58; AMA Br. 9-11, 13-15. Yet the manner in which Myriad has used its patents – as well as the positive impact that Myriad has had among patients, physicians, and researchers – belies that notion.

A. Increased Awareness Of BRCA Testing Among Physicians And Patients Confirms The Wisdom Of Allowing Patents On Genetic Material.

Petitioners and their amici suggest that allowing genetic material to be patented means that the technology will languish in a dark corner, with the public unable to reap the technology's benefits. *See, e.g.*, Pet. Br. 56-58; AMA Br. 13-15. Myriad's activities with respect to the BRCA1 and BRCA2 patents over the past two decades cast serious doubt on that conjecture.

Perhaps most significantly, Myriad has raised awareness of BRCA testing among physicians and patients. The record in this case reflects that, as the holder of patents on BRCA1 and BRCA2, Myriad invested over $200 million in awareness campaigns and education programs. Decl. of Mark Skolnick, Ph.D., J.A. 502. These efforts included establishing a 300-person sales force to call oncologists, surgeons, and OB/GYNs across the country to discuss the benefits of BRCA testing and personally meet with medical professionals to answer questions. Decl. of Gregory Critchfield, M.D., J.A. 345. Myriad also organized over three hundred "speaker programs," which have provided physicians with the opportunity to learn about BRCA testing from leaders in their field and discuss it with their peers. *Id.* at 345-46. Critically, as part of these programs, the company employed well-trained and well-versed genetic counselors who did not simply push BRCA testing, but ensured that physicians understood the testing process so they could determine when it was appropriate to recommend it to patients. *Id.* at 345.

Myriad's efforts have helped to fill a problematic gap in physicians' knowledge about genetic testing. It is vital that physicians be fully aware of the medical and ethical implications of BRCA testing before recommending it to a patient. Yet as recently as 2006, many physicians lacked basic knowledge about such testing despite regular inquiries from their patients. Melanie F. Myers et al., *Genetic Testing for Susceptibility to Breast and Ovarian Cancer: Evaluating the Impact of a Direct-to-Consumer Marketing Campaign on Physicians' Knowledge and Practices*, 8 Genet. Med, 361 (2006). Myriad's efforts helped remedy this situation; physicians in cities where the company ran marketing campaigns were more than twice as likely to have received educational materials about BRCA testing. *Id.* at 363. More informed doctors provide better advice to their patients and, according to another recent study, are twice as likely to order genomic testing as their less-informed peers. *Physician Survey Shows Education Big Factor in PGx Adoption*, GenomeWeb (Oct. 23, 2009), http://www.genomeweb.com/dxpgx/physician-survey-shows-education-big-factor-pgx-adoption. By educating physicians, Myriad has ensured that BRCA testing becomes an integral part of the battle against breast and ovarian cancer.

In addition to raising awareness among physicians, the record here establishes that Myriad has devoted millions of dollars to educating patients about BRCA testing. Critchfield Decl., J.A. 346. Through advertisements on television and in other mass media, the company has offered information about hereditary breast and ovarian cancer and encouraged at-risk patients to speak with their physicians to determine if BRCA testing is appropriate. *Id.* These advertisements were designed to effectively convey the importance of BRCA testing to healthy family members of cancer patients. *Id.*; *see also* DGR Evans et al., *Comparison of Proactive and Usual Approaches to Offering Predictive Testing for BRCA1/2 Mutations in Unaffected Relatives*, 75 Clin. Genet. 124 (2009) (discussing the effectiveness of proactive approaches to patient education). The advertisements ran nationwide, including in remote rural areas. Critchfield Decl., J.A. 346. As a result of these and other efforts to raise public awareness of the availability of BRCA testing, almost one million patients nationwide have undergone such testing. Critchfield Decl., J.A. 346-47; *Brief History of Myriad*, Myriad Genetics, http://www.myriad.com/about-myriad/history/ (last visited Mar. 12, 2013).

Beyond the sheer number of people who have received BRCA testing, several studies confirm that Myriad's patient-directed campaigns have increased awareness of BRCA testing among the very people who are most at risk. For example, one group of researchers studied the impact of an intensive five-month, direct-to-consumer Myriad awareness campaign. Jan T. Lowery et al., *The Impact of Direct-to-consumer Marketing of Cancer Genetic Testing on Women According to Their Genetic Risk*, 10 Genet. Med. 888 (2008). The campaign was targeted at women between the ages of 25 and 54, especially those with a family history of breast cancer. *Id.* at 888. After the campaign was completed, the researchers took extensive surveys, and concluded that women with an increased genetic risk were more likely to recall seeing Myriad's advertisements than women who were less appropriate candidates for BRCA testing. *Id.* at 892. Moreover, nearly half of the high-risk women who recalled encountering the advertisements stated they were more interested in testing. *Id.* Other studies have confirmed this outcome, and demonstrate that Myriad's awareness campaigns effectively encourage testing among patients vulnerable to breast cancer. *See, e.g.*, Judy Mouchawar et al., *Impact of Direct-to-Consumer Advertising for Hereditary Breast Cancer Testing on Genetic Services at a Managed Care Organization: A Naturally-Occurring Experiment*, 7 Genet. Med. 191 (2005); Centers for Disease Control and Prevention, *Genetic Testing for Breast and Ovarian Cancer Susceptibility: Evaluating Direct-to-Consumer Marketing – Atlanta, Denver, Raleigh-Durham, and Seattle, 2003*, MMWR Wkly. Rep. (July 16, 2004), *available at* http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5327a1.htm.

The evidence from multiple BRCA awareness studies is clear. Myriad, the holder of the BRCA patents, has significantly increased awareness of the BRCA test's utility. And it has done so both among physicians and among patients, including those at highest risk. Indeed, because of the potential for "free riders," it is hard to imagine a single company undertaking such massive educational efforts without the exclusivity conferred by a patent.

B. Myriad's Activities Demonstrate That Patenting Genetic Material Does Not Price Patients Out Of Testing.

The AMA's brief criticizes genetic patents on the ground that they supposedly inflate the price that a patient must pay for testing. AMA Br. 11-13. In this way, the argument goes, such patents place genetic testing out of reach for many who would benefit from it. Once again, the record does not support these assertions.

The record here establishes that Myriad has made BRCA testing broadly available to patients nationwide. The company has worked to maximize the number of insurance plans that cover BRCA testing; to date, Myriad has established over 400 contracts with private insurance companies, state-run Medicaid programs, and Medicare. Critchfield Decl., J.A. 347-48; *see also* E. Richard Gold & Julia Carbone, *Myriad Genetics: In the Eye of the Policy Storm*, 12 Genet. Med. S39, S42 (2010) (discussing Myriad's efforts to build a network of insurers). Since July 2007, patients have thus received reimbursement for testing under more than 80,000 insurance plans across the country, paying average out-of-pocket costs of less than $100. Critchfield Decl., J.A. 348. Acknowledging that insurance is not universally available, Myriad has also implemented a financial assistance program that provides free testing to low-income, uninsured patients. *Id.* As a result of these efforts, *approximately 95% of all* *patients* in the United States have access to BRCA testing. Press Release, Myriad Genetics, *Supreme Court of the United States to Hear Isolated DNA Patent Case* (Nov. 20, 2012), http://investor.myriad.com/releasedetail.cfm?ReleaseID=724300.

To be sure, there may well be instances in which cost prevents a patient from undergoing BRCA testing. But in a fee-for-service health care system, there always will be some patients who are priced out of particular treatments or diagnostics. And to the extent that high costs to consumers result from the fact that the isolated BRCA genes are patented, the same could easily be true of any *other* patented medical technology. There is no reason to think that *gene* patents are particularly likely to have this effect. Indeed, the evidence suggests that the patents at issue in this case have *not* inflated the prices that patients pay for genetic testing. To the contrary, Myriad has striven to keep its rates commensurate with companies offering other types of full-sequence genetic testing – regardless of whether patents are involved. Critchfield Decl., J.A. 349.

Consistent with these efforts, studies have found no obvious price premium attributable to Myriad's exclusive patent rights. One recent study examined the prices charged by different companies for a variety of genetic tests. *See* Robert Cook-Deegan et al., *Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers with Colon Cancers*, 12 Genet. Med.

S15 (2010). The researchers took particular interest in comparing the cost of BRCA testing and Lynch Syndrome testing, the latter of which is covered by patents that are not enforced.[2] *Id.* at S20-22. Despite acknowledging fears that Myriad would use its monopoly to overcharge patients for BRCA testing, *id.* at S28-29, the study found no clear link between the costs of genetic testing and the existence of exclusive patent rights. *Id.* at S30. Specifically, it found that "prices for BRCA1 and 2 testing do not reflect an obvious price premium attributable to exclusive patent rights . . . and indeed, Myriad's per unit costs are somewhat *lower* for BRCA1/2 testing than testing for colorectal cancer susceptibility." *Id.* at S15 (emphasis added). The same year, an NIH draft report reached a similar conclusion: "no evidence was found that patents and exclusive licenses have consistently led to higher prices for genetic tests." National Institutes of Health, Office of Biotechnology Activities, *Revised Draft Report on Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests* 35, Feb. 2, 2010, *available at* http://oba.od.nih.gov/oba/SACGHS/

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[2] Lynch Syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), is the most common type of inherited colorectal cancer. R. Cook-Deegan et al., 12 Genet. Med. at S20. As with breast cancer, certain genes predispose an individual to developing Lynch Syndrome. *Id.* at S20. But unlike BRCA, the Lynch Syndrome gene patents were filed by universities and never enforced. Accordingly, a variety of providers, including Myriad, offer patients Lynch Syndrome testing. *Id.* at S21.

SACGHS%20Patents%20Report%20Approved%202-5-20010.pdf.

The importance of Myriad's awareness campaigns and efforts to keep BRCA testing affordable cannot be understated. These two endeavors have created a framework in which women can easily learn about BRCA testing, can consult with knowledgeable physicians to determine if testing is appropriate for them, and face little economic hardship if they decide to proceed. All of this suggests that patents on isolated human genes do not, in fact, have the adverse consequences that petitioners and their amici assert.

C. The History of Myriad's Patents Confirms that Gene Patents Do Not Unduly Impede Scientific Research.

Besides arguing that gene patents somehow impede access to health care, petitioners and their amici also contend that they constrain scientific and medical research. *See, e.g.*, Pet. Br. 56-58; AMA Br. 13-15. But, as an initial matter, such constraints are inherent in our patent system, which provides that in exchange for disclosure of his or her invention, the inventor has the time-limited right to exclude others from practicing that invention – even if they wish to practice it to achieve further innovation. *See, e.g.*, *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 150-51 (1989) ("The federal patent system thus embodies a carefully crafted bargain for encouraging the creation and disclosure of new, useful, and nonobvious advances in technology and design in return for the exclusive right to practice the invention."). Thus, all medical and scientific patents, at some basic level, have the potential to constrain research for a period of time.

In any case, the record shows that the patents here have not had the harmful effects on research that petitioners and their amici claim. By way of background, the development of BRCA testing was itself a significant advancement in cancer research – and one that likely could not have been achieved without the promise of patentability. Myriad was founded because a group of experienced, talented scientists could not receive adequate public funding to pursue their search for BRCA1. Skolnick Decl., J.A. 500. In its early years, Myriad relied heavily on large investments from venture capitalists and corporate collaborators. *Id.* at 500-01. Fueled by these resources, as well as "a spirit of cooperation, urgency, and camarader[ie] . . . that is rare in academia," the Myriad team broke new ground by discovering BRCA1 in 1994. *Id.* at 501. Subsequently, Myriad discovered BRCA2 in late 1995, and in doing so corrected serious errors in a proposed structure of that gene that a competitor was seeking to patent. *Id.* at 500; Decl. of Sean Tavtigian, J.A. 507-09; *see also* Gold & Carbone, 12 Genet. Med. at S41-42 (discussing the origins of Myriad and the company's early discoveries). If not for Myriad, it is uncertain when BRCA1 testing would have become available, or if the patented BRCA2 structure would remain forever flawed.

In the years since Myriad discovered the BRCA genes, the company has continued to make significant contributions in the field of cancer research. Myriad has published well over 100 articles in peer-reviewed journals and scientific meetings, and helped build a comprehensive central online repository for information on BRCA mutations. Critchfield Decl., J.A. 335; Breast Cancer Information Core, Nat'l Human Genome Research Inst., http://www.research.nhgri.nih.gov/bic/ (last visited March 12, 2013). The company also adopted an expansive collaboration policy with far-reaching benefits in the cancer research community. For example, Myriad has worked with hundreds of outside researchers and participated in more than 100 outside programs and studies since 1994. Critchfield Decl., J.A. 333. Acting under similar principles, the company has facilitated external research by providing genetic materials for free to researchers at over 30 institutions, and by signing a Memorandum of Understanding with the National Cancer Institute to provide discounted research testing services to scientists. *Id.*; Tom Reynolds, *NCI-Myriad Agreement Offers BRCA Testing at Reduced Cost*, 92 J. Nat'l Cancer Inst. 596 (2000).

To be sure, certain plaintiffs in this case contend that they personally have been deterred from pursuing research because of genetic patents. *See, e.g.*, Decl. of Ellen T. Matloff, J.A. 623; Supp. Decl. of Harry Ostrer, J.A. 722-23. Neutral studies, however, indicate that such deterrence is uncommon. As one recent survey of such studies concluded, there is no evidence that genetic patents "acted as a research impediment in the past 30 years," and "[t]he number of reported patent lawsuits involving gene patents is practically nonexistent." Jim Greenwood, *Gene Patents Do Not Hinder Academic Research*, 9 Nature Methods 1039 (2012); *see also* CJ Murdoch & Timothy Caulfield, *Commercialization, Patenting and Genomics: Researcher Perspectives*, 1 Genet. Med. 22, 22.4 (2009) ("[L]ittle is said to suggest that the progress of research itself is in fact being seriously hindered. . . . [T]here is [also] little evidence that gene patents are being aggressively enforced."); John P. Walsh et al., *View from the Bench: Patents and Material Transfers*, 309 Science 2002, 2003 (2005) ("Our results offer little empirical basis for claims that restricted access to IP is currently impeding biomedical research."); Decl. of Joseph Straus, J.A. 571-75. Legal experts examining the topic, for their part, have similarly concluded that there is little reason to fear that genetic patents will stifle medical or scientific advancement. *See* Christopher M. Holman, *Will Gene Patents Derail the Next Generation of Genetic Technologies?: A Reassessment of the Evidence Suggests Not*, 80 UMKC L. Rev. 563, 605 (2012) (arguing that genetic patents do not hinder research and that more patent protection may be needed); W. Nicholas Price II, *Unblocked Future: Why Gene Patents Won't Hinder Whole Genome Sequencing and Personalized Medicine*, 33 Cardozo L. Rev. 1601, 1631 (2012) (concluding that genetic patents are far less significant barriers to whole-genome sequencing or personalized medicine than is sometimes assumed).

D. Myriad's Promotion and Use of Its Patents Has Benefited Practicing Physicians and Their Patients.

In the course of practice, amici have observed the benefits and evolution of BRCA testing. Before Myriad obtained its patents and began offering a way of detecting BRCA mutations, physicians could provide few answers to patients about their individual risk of developing breast and ovarian cancer. Although family history provided some clues about a patient's vulnerability, the science was far from exact. *See* Martha L. Slattery & Richard A. Kerber, *A Comprehensive Evaluation of Family History and Breast Cancer Risk: The Utah Population Database*, 270 J. Am. Med. Ass'n 1563 (1993). This posed serious problems for patients deciding whether prophylactic treatment was appropriate, especially given the surprisingly high rate of mammographic errors and unnecessary mastectomies performed each year. *See* Wendie A. Berg, L. Gutierrez, et al., *Diagnostic Accuracy of Mammography, Clinical Examination, US, and MR Imaging in Preoperative Assessment of Breast Cancer*, 233 Radiology 830 (2004); Stephanie Saul, *Prone to Error: Earliest Steps to Find Cancer*, N.Y. Times, July 19, 2010, at A1. The advent of BRCA testing, however, radically changed this situation for the better.

BRCA testing has allowed amici and other physicians to provide their patients with a clearer understanding of their risk of cancer. Specifically, if a patient's BRCA test is positive, physicians can alert her that there is a significant chance that she will develop breast or ovarian cancer and can provide personalized preventative treatment. Sining Chen & Giovanni Parmigiani, *Meta-Analysis of BRCA1 and BRCA2 Penetrance*, 25 J. Clinical Oncology 1330 (2007); *see also* Donald Aptekar, *Why I Test My Patients*, Learn About HBOC, http://learnabouthboc.com/stories/ (last visited Mar. 12, 2013). In this way, BRCA testing allows physicians to better assist the rapidly growing number of young women who develop advanced breast cancer, and ultimately, to save lives. *See* Denise Grady, *Study Sees More Breast Cancer at Young Age*, N.Y. Times, Feb. 27, 2013, at A13.

Amici view the increasing awareness of BRCA testing among physicians and patients as an indisputably positive trend, and credit Myriad for effectively promoting its patents. Prior to Myriad's awareness campaigns, few practicing physicians were informed of the benefits or availability of BRCA testing. *See* Critchfield Decl., J.A. 344-45. Now, amici and thousands of their colleagues regularly rely upon BRCA testing in counseling and treating patients. This revolution was largely facilitated by Myriad, which has encouraged discussion about genetic testing between doctors and at-risk patients.

In amici's experience, moreover, Myriad's tests are of the highest quality. The company's status as the sole provider of BRCA testing has provided it with an unparalleled genetic library. As a result, Myriad (in amici's experience) provides fewer inconclusive results, and is able to provide better information than companies that compete to provide other types of genetic tests. *See also* Charis Eng et al., *Interpreting Epidemiological Research: Blinded Comparison of Methods Used to Estimate the Prevalence of Inherited Mutations in BRCA1*, 38 J. Med. Genet. 824 (2001) (validating the accuracy of Myriad's testing methods); Critchfield Decl. 350-55. Amici thus consider Myriad to be the most reliable genetic testing provider in the United States, and view the company's BRCA patents as an asset for their patients.

II. PATENTING GENETIC MATERIAL IS NOT INHERENTLY UNETHICAL.

The AMA's brief urges that genetic patents – which have helped hundreds of thousands of patients worldwide – are inherently unethical. *See* AMA Br. 36-37. The brief argues that "physicians' and scientists' ethical duties recognize that laws of nature and products of nature must be treated as prior art and shared to benefit the public and to encourage innovation." *Id.* at 37. Yet as discussed above, there is little empirical evidence to support the claim that genetic patents hinder research or scientific advancement. *See* Greenwood, 9 Nature Methods at 1039. Even more problematically, the AMA's position elevates hypothetical concerns over the realities that medical professionals face on a daily basis. As the AMA itself recognizes, practicing physicians have an ethical obligation to provide their patients with the best care possible: "The relationship between patient and physician[s] is based on trust and gives rise to physicians' ethical obligations to place patients' welfare above their own self interest and above obligations to other groups, and to advocate for their patients' welfare." Am. Med. Ass'n Ethics Opinion 10.015, The Patient-Physician Relationship. Particularly in view of Myriad's responsible stewardship of the patents implicated by BRCA testing – which has undoubtedly saved countless lives – the AMA's across-the-board condemnation of genetic patents is indefensible.

That condemnation is also questionable, moreover, in light of the rapidly shifting views of ethics in the field of genetics. Over the past thirty years, scientists and academics have often decried nascent genetic technologies as unethical. But what was initially condemned has often found widespread acceptance. For example, paternity testing and in vitro fertilization (IVF) were ethically scrutinized when they first became available to the public, only to become widely accepted a few short years later. *See* Ronald Bailey, *Warning: Bioethics May Be Hazardous to Your Health*, Reason (Aug./Sept. 1999), *available at* http://reason.com/archives/1999/08/01/warning-bioethics-may-be-hazar. Likewise, when this Court was considering the patentability of microorganisms, scientists offered a "gruesome parade of horribles," "suggesting that genetic research may pose a serious threat to the human race." *Diamond v. Chakrabarty*, 447 U.S. 303, 316 (1980). The patents were nevertheless upheld, and three decades later, none of the dire forecasts have come to fruition. *See* Holman, 80 UMKC L. Rev. at 599.

Indeed, the story of BRCA testing itself confirms that ethical views are liable to shift over time. When BRCA testing was first made available, some argued that it was unethical to inform patients whether they carried the genes. Bailey, *Warning*; *see also* Danielle Simmons, *Bioethics in Genetics*, 1 Nature Educ. 1 (2008), *available at* http://www.nature.com/scitable/topicpage/bioethics-in-genetics-42093; Francis S. Collins, Director, Nat'l Center for Human Genome Research, Statement on Advances in Genetic Research and Technologies: Challenges for Public Policy before the S. Comm. on Labor and Human Resources (July 25, 1996), *available at* http://www.genome.gov/10002351. If enshrined in law, this paternalistic view would have drastically limited a patient's ability to make informed decisions about issues of literally vital medical importance. Fortunately, it became accepted practice for physicians to share and discuss BRCA test results with their patients. Given this background, it would be the height of irony to now condemn genetic patents as unethical. *See* Ronald Bailey, *Gene Testing Irony: Once Restricted, Now a Right?*, Reason.com Hit & Run Blog (Apr. 2, 2010, 3:05 pm), http://reason.com/blog/2010/04/02/gene-testing-irony-once-restri.

As this Court explained in upholding the validity of patents on microorganisms, when faced with controversial policy choices, the judiciary must neither "brush them aside as fantasies generated by fear of the unknown, [n]or . . . act on them." *Diamond*, 447 U.S. at 317. Rather, the ethics of genetic patents are a "matter of high policy for resolution within the legislative process after the kind of investigation, examination, and study that legislative bodies can provide and courts cannot." *Id*

CONCLUSION

The judgment of the Federal Circuit should be affirmed.

Respectfully submitted,

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March 14, 2013

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CURIAE
BRIEF

Supreme Court, U.S.
FILED
JAN 30 2013
OFFICE OF THE CLERK

No. 12-398

In the Supreme Court of the United States

ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,
Petitioners,
v.
MYRIAD GENETICS, INC., ET AL.,
Respondents.

ON WRIT OF CERTIORARI TO
THE UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

BRIEF OF GENEDX AND LAW PROFESSORS AS *AMICI CURIAE* IN SUPPORT OF PETITIONERS

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ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,
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BRIEF OF GENEDX AND LAW PROFESSORS AS *AMICI CURIAE* IN SUPPORT OF PETITIONERS

INTEREST STATEMENT OF *AMICI CURIAE*

Amici are GeneDx and law professors whose scholarship and teaching focuses on patent law and related fields.[1] *Amicus* GeneDx is a diagnostic laboratory that was started for the purpose of providing molecular diagnoses for patients and families with rare and ultra-rare hereditary disorders. The company was formed by National Institutes of Health (NIH) scientists who wished to provide diagnostic services to the families with histories of genetic disorders. GeneDx has discovered several genes linked to rare skin disorders and has never attempted to patent such genes. As long as the federal courts uphold patents on human genes linked to disorders that NIH scientists or patients wish tested, GeneDx is unable to assist such families. The small market for rare disorder testing services, combined with the large investment in time and effort to develop new tests, makes paying license fees to gene patent owners an absolute deterrent to developing diagnostics for patients suffering from most rare disorders. Gene patents have accordingly had a negative impact on the development and availability of genetic tests for patients and families, especially those with rare disorders.

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[1] Pursuant to this Court's Rule 37.6, no counsel for a party authored this brief in whole or part, and no person or entity made any monetary contribution to the preparation or submission of the brief. The petitioners in this case have filed a letter giving blanket consent to the filing of *amicus* briefs in this case. The respondents have specifically consented to the filing of this *amicus* brief.

Amici law professors are Linda J. Demaine, Aaron X. Fellmeth, and Dennis Karjala, Professors of Law at the Arizona State University, Sandra Day O'Connor College of Law. Law faculty have an interest in ensuring that the Patent Act is interpreted to reflect accurately the constitutional limits on Congress's power to grant patents, the historical underpinnings of U.S. patent law, and the public policies the Constitution and Patent Act seek to promote.

SUMMARY OF ARGUMENT

The U.S. Constitution grants Congress no power to issue patents on products of nature, nor has Congress sought to exercise such a power. The Supreme Court has accordingly held patents on natural phenomena invalid long and consistently. Scientific and technological innovation has benefited from this policy.

However, the policy has come under threat by the U.S. Patent and Trademark Office (PTO) and certain federal courts, which have granted and upheld patents on "isolated," natural human genes as well as cDNA copies of them. Such genes and cDNA are products of nature regardless of whether they have been "purified," removed from larger molecules, or synthesized using well-known methods to copy the coding portions of natural human DNA.

Judge Lourie's opinion below treats natural human DNA as if it were an industrial chemical whose physical structure determines its properties. He treated the human chromosome as the relevant molecule, so that any natural chemical contained in that chromosome is not a "product of nature," in his opinion.

This conclusion reflects a fundamental misconception about DNA molecules. Living DNA cannot be compared to inert industrial chemicals. DNA molecules and chromosomes may have identical physical structures while producing wildly different proteins and other biochemicals; it is the order of nucleotides that determines the gene's biological function. One who merely replicates the order of nucleotides by "isolating" a gene or part of a gene is claiming the essence and *raison d'être* of the gene. All protein-coding genes exist to express proteins; by claiming the natural sequence of DNA coding for a natural protein, a patent applicant claims a portion of the blueprint of life itself.

The Federal Circuit also relied on a lower court decision from 1911, holding that when a product of nature has been so altered to have greater therapeutic or commercial value, it becomes patentable subject matter. Although lower courts have increasingly relied on this theory, it is the wrong standard for determining the patentability of products of nature. This Court has never held, and should not hold, that some human intervention that increases the inherent therapeutic or commercial value of a product of nature *ipso facto* justifies treating the result as a new and distinct product susceptible to patenting.

Instead, the Court should continue to hold that a product of nature must be transformed into a new article with a markedly different name, character, and use to qualify as patentable subject matter. As this "substantial transformation test" applies to human DNA, "isolated" genes fail to qualify as patentable subject matter. The essence of a human gene is its ability to express a specific protein; therefore, any molecule that merely extracts or copies the gene's sequence of nucleotides to express that same protein is insufficiently different from the natural gene. If the new molecule performs the same biological function as the natural gene, it is the same product of nature.

By similar logic, a cDNA molecule that merely copies the protein-coding portions of a human gene (exons) is a gene with its regulatory nucleotide sequences omitted. It performs precisely the same biological function as the natural and "isolated" genes, in the same way, and merely represents an attempt to patent the natural gene. Moreover, the concept of omitting the non-coding region of a DNA molecule (introns) is not a human innovation, it is a well-known natural process. Messenger RNA, a natural molecule used in the process of gene translation, is a single-stranded copy of the gene with the introns omitted. A cDNA is "synthetic" only in the sense that it is a double-stranded version of the mRNA molecule, with the complementary strand dictated by the same laws of nature that dictate DNA's complementary strand. There is nothing remotely inventive about it.

If products of nature are unpatentable subject matter, biologically insignficant modifications to products of nature should also be unpatentable. The substantial transformation test draws a reasonably bright line between insignificantly altered products of nature and man-made inventions; is consistent with Supreme Court precedent; and avoids the many negative repercussions of patents that confer an effective monopoly on fundamental biological components of the human body.

ARGUMENT

I. Products of nature are not patentable subject matter.

The U.S. Constitution authorizes Congress to grant patents only to "Inventors" for their "Discoveries." U.S. CONST. art. 1, sec. 8, cl. 8. The term "discoveries," as used in this clause, is a term of art. It refers not to preexisting facts that any person might come upon, but rather as a synonym for "inventions," being the product of human ingenuity. *See* Linda Demaine & Aaron Fellmeth, *Reinventing the Double-Helix*, 55 STAN. L. REV. 303, 367-74 (2002). The Constitution thereby establishes that a newly discovered product of nature is not patentable subject matter, because it was not "invented" by any person.

Consistent with this limitation on congressional power, Congress drafted the 1952 Patent Act to authorize a patent on any "new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." 35 U.S.C. § 101. Newly perceived products of nature are by definition not "new," but preexist the human perception of them. Although Congress has several times considered amendments to the Patent Act that touch on the question of whether products of nature are patentable, such as the Plant Patent Act of 1930, 46 Stat. 703, ch. 497, *codified as amended at* 35 U.S.C. §§ 161-64, it has never endorsed the patenting of natural phenomena of any kind.

This Court has accordingly long held that patents may not be granted on products of nature. *E.g.*, *Diamond v. Chakrabarty*, 447 U.S. 303, 309, 313 (1980). Never has the Court strayed from this firm rule. "[T]o transform an unpatentable law of nature into a patent-eligible *application* of such a law, one must do more than simply state the law of nature while adding the words 'apply it.'" *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289, 1294 (2012).

That the discovery of a product of nature may have been difficult, costly, uncertain, and scientifically groundbreaking is and has always been irrelevant. "Products of nature are nonstatutory subject matter. This defect cannot be remedied by a showing of novelty, utility, or non-obviousness." John M. Conley & Robert Makowski, *Back to the Future: Rethinking the Product of Nature Doctrine as a Barrier to Biotechnology Patents (Part II)*, 85 J. PAT. & TRADEMARK OFF. SOC'Y 371, 391 (2003). In any case, genes are not difficult, costly, or uncertain to discover. Using modern sequencing technology, the entire human genome can now be sequenced with certainty within a week at the cost of a few thousand dollars.

This conclusion is consistent with the policies the Framers sought to promote in the Constitution's Intellectual Property Clause. Products of nature, thought as yet undiscovered, exist in the public domain; they are *res communis*, "free to all men and reserved exclusively to none." *Chakrabarty*, 447 U.S. at 309. They are elemental components of the physiology of living organisms, a functioning ecology, or the chemistry of the universe. The innate curiosity of *homo scientificus* and the structure of universities, which reward faculty and students finding new facts about nature, together provide sufficient incentive to research natural phenomena. No patent incentive is generally required for such fundamental discoveries. Moreover, because products of nature are the fundamental building blocks of all matter and life, a patent on a product of nature risks investing the patentee with a power to tax or entirely prevent research on vast and uncharted fields of knowledge. Such a power may generally be expected to extend far out of proportion to the effort and insight invested in discovering the product of nature.

II. Human genes, including isolated human DNA sequences, are products of nature unless transformed into a new product with a different biological function.

That an "isolated" human gene remains a product of nature is evident from the fact that the person claiming such a gene "invented" nothing. He merely used well-known techniques for severing a string of nucleic acids from their surrounding chromosomal matrix. In fact, it is perfectly possible to obtain a patent without even having performed the act of severing the gene from the chromosome; success in "isolating" the gene is so certain using standard laboratory techniques that a patent applicant need merely sequence the gene (as discussed below, also using well known and mostly automated techniques invented by others) and submit the patent application claiming the "isolated" gene as an "invention." Yet, there is no invention in isolating a gene, and without invention, Congress has no power to grant a patent under the Constitution.

Nonetheless, some 30 years ago, the U.S. Patent and Trademark Office (PTO) began granting patents on human genes in their natural state, with the word "isolated" affixed to the claim. Judge Lourie of the U.S. Court of Appeals for the Federal Circuit believes that isolated human DNA is patentable subject matter, because is it not "found in nature" as such. *Association for Molecular Pathology v. United States Patent & Trademark Office*, 689 F.3d 1303, 1325 (Fed. Cir. 2012). His and Judge Moore's opinions seem to recognize that, to constitute patentable subject matter, an invention must be "man-made," "the product of human ingenuity," "markedly different" from what exists in nature, and have a "distinctive name, character, and use." *Id.* at 1325-26, 1329 (Lourie, J.), 1339 (Moore, J.).

These opinions also admit that an "isolated" human protein-coding gene contains the same biological information (that is, it codes for the same protein) as the natural gene existing in the human body. Like that natural gene, the isolated DNA sequence serves the sole biological function of expressing a specific protein. However, Judge Lourie believes that isolated genes qualify as patentable subject matter because they have a "distinctive chemical structure." *Id.* at 1328. By this, he means that a "chemical" is defined as a group of atoms covalently bonded to one another; by severing some of those bonds, a person creates a different "chemical." Because in nature a DNA molecule is "intertwined with various proteins," under this view, a chromosome is a single "molecule." *Id.* Based on this belief, Judge Lourie reasoned that "isolated" natural DNA satisfies this Court's precedents distinguishing products of nature from patentable inventions, because the isolated DNA has been cleaved from the chromosome by human intervention. *Id.* at 1328, 1330; *see also id.* at 1341-42 (Moore, J., concurring). Judge Moore further concluded that this chemical manipulation satisfies the criteria for a 1911 lower court decision, *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95 (C.C.S.D.N.Y. 1911), , *aff'd in part, rev'd in part*, 196 F. 496 (2d Cir. 1912), presumably because the isolated gene has commercial uses to which the natural gene cannot be put while remaining in the chromosome.

These opinions make much of the "human intervention" involved in isolating DNA from the chromosome, calling the resulting product "man-made" repeatedly throughout. However, neither opinion argues that human intervention alters the biological use of the DNA in the claims at issue. The opinions try to minimize the significance of DNA's biological function, calling it "irrelevant," and preferring to focus on the differences between the chemical structure of the assumed product of nature (a chromosome) and the chemical structure of the much smaller, isolated (or "purified") gene. *See Association for Molecular Pathology*, 689 F.3d at 1330 (Lourie, J.), 1343 (Moore, J.).

These opinions are correct in asserting that an isolated gene is a product of human intervention, in much the same way that (as Judge Bryson put it) a kidney is the product of human intervention when excised from a human body. *Id.* at 1352-53 (Bryson, J., concurring in part and dissenting in part). But the input of skill and labor no more takes kidneys out of the realm of products of nature when "isolated" than does the DNA sequence of nucleotides. The fact that removing the nucleotides is performed by a geneticist or biochemist "in the laboratory," *id.* at 1325, is no more significant than the fact that the isolation of the kidney is performed by a surgeon in an operating room.[2] Nor does the "skill, knowledge, and effort" required to isolate the DNA matter, *id.* at 1332, if the result is a product of nature (although the process of isolating it may well be patentable subject matter). In any case, as noted, sequencing and isolating a human gene has long been well within the skill of any ordinary biochemist.

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[2] One especially egregious error Judge Lourie made in rejecting this comparison was to suggest that removing a human kidney requires little skill, knowledge, or effort. *Id.* at 1332. He is greatly underestimating both the difficulties of surgery and the ease of sequencing and isolating DNA. It is especially ironic that he tried to buttress his argument that courts should let sleeping dogs lie by noting that the PTO issued 2,645 patents claiming isolated DNA over the past twenty-nine years. The number leaps to 40,000 if DNA-related patents of human genes are included, according to his opinion. If DNA requires such exceptional knowledge, skill, and effort to sequence and isolate, it is strange that there should be such a massive proliferation of DNA patents.

The argument that removing DNA from a chromosome is distinguishable because it converts the DNA to a "different molecular entity" misses the point. The gene is not merely an inert "chemical entity" like sodium chloride or ammonia, it is a biological component, an integral, defining, and biologically *functional* part of human life. Its physical structure does not define it; different chromosomes and genes can have the identical macrostructures while having radically differing functions. A gene is defined by its sequence of nucleotides. It is composed of an arrangement of nucleotides that, in the specific order they exist in nature, expresses a specific protein or RNA product. A change to that order is likely to change the protein. Expressing a specific protein is the very reason for the protein-coding gene's existence. To claim the sequence of nucleotides coding for the protein is to claim the natural gene and its biological function. It is to claim a portion of life's blueprint.

Judge Moore's attempt to distinguish a patent on a natural product like a human kidney from a patent on an isolated gene fails as well. The *Parke-Davis* case does not set forth the correct standard for invention. *Parke-Davis* relied on the fact that the patent applicant had done something to confer greater therapeutic and commercial value on the product of nature as the basis for accepting the resulting "purified" chemical as a new, synthetic product. But increasing a natural product's therapeutic or commercial value does not automatically make the resulting product patentable subject matter. The excised kidney, like the isolated gene, is "for every practical purpose a new thing commercially and therapeutically," *Parke-Davis*, 189 F. at 103, *quoted in Association for Molecular Pathology*, 689 F.3d at 1339. A kidney removed from a human body can be used as a life-saving transplant; one currently in a body cannot. The attempt to distinguish the cases is strained and unconvincing.

This Court has long and consistently denied the patentability of natural phenomena that have been insignificantly altered. *See Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289 (2012) (correlation between the presence of drug in the bloodstream and the biologically effective dosage of the drug); *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1, 11-12 (1931) (natural fruit treated with mold-resisting chemical); *cf. Winans v. Denmead*, 56 U.S. (15 How.) 330, 341 (1853) ("Under our law a patent cannot be granted merely for a change of form.... Merely to change the form... is the work of a constructor, not of an inventor; such a change cannot be deemed an invention."). A policy of awarding patents for minor alterations of a product of nature improves in no way on a policy of allowing patents on products of nature. A patent applicant may be expected to make trivial alterations to natural products in order to bring them within the scope of patentable subject matter or adapt them to commercial needs. *De minimis non curat lex* "is part of the established background of legal principles against which all enactments are adopted, and which all enactments (absent contrary indication) are deemed to accept." *Wisconsin Department of Revenue v. William Wrigley, Jr., Co.*, 505 U.S. 214, 231 (1992).

A certain line of district and appellate court cases, illustrated by Judge Learned Hand's opinion in *Parke-Davis* and on which Judge Moore especially relied, has contradicted this Court's doctrine denying the patentability of minor variants of products of nature. *See generally* Demaine & Fellmeth, *supra*, at 334-39 (describing the line of cases). In *Parke-Davis*, the district court held that a new process for purifying the human hormone adrenaline could justify a product patent on the resulting relatively pure adrenaline, because the purer adrenaline was therapeutically and commercially more valuable than less pure adrenaline. 189 F. at 102-03. *Parke-Davis* conflated the invention of a process with the invention of its resulting product in weighing the ingenuity of the purification process in favor of the the ingenuity of the resulting product. It also conflated the utility of an innovation with its patentability. The relevant question is not whether some modicum of human intervention has conferred greater therapeutic or commercial value on a product of nature. As noted above, a kidney does not become commercially or therapeutically valuable until removed from the human body, but its removal does not render it patentable subject matter. The pertinent question is whether it has transformed the product of nature into a new and markedly different product with a distinctive name, character, and use.[3] *Diamond v. Chakrabarty*, 447 U.S. 303, 309-10 (1980).

This Court has never held, and should not now hold, that a new-found product of nature becomes patentable merely because a human act has given it more practical or commercial utility, or even a different overall chemical structure. On the contrary, in *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948), this Court decisively rejected the argument that minor alterations to a product of nature rendered it patentable. In that case, the patentee had packaged together several strains of naturally occurring plant-inoculating bacteria. The patent was based on the discovery that, although many strains of inoculating bacteria inhibit each other from assisting plants in fixing nitrogen for growth and metabolism when combined, certain strains had no inhibitory effect on other strains and could usefully be packaged together as an inoculant for multiple crops. The applicant accordingly claimed a combination of natural bacteria. The Court held that, because the bacteria continued to perform their natural function in the way they always had, the patent applicant had not invented a patentable product.

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[3] In *Chakrabarty*, this Court used the classic customs law formulation "name, character, and use," but, as discussed in Demaine & Fellmeth, *supra*, at 394-95, a change in name serves at most as an indirect and unreliable indicator of change in character and use.

The *Funk Brothers* decision was based on the recognition that allowing patents on insubstantial modifications of products of nature does not serve the patent law's goal of encouraging innovation. Although it is reasonable to take issue with the application of that principle on the facts before the Court at that time, the fundamental premise is sound. *Funk Brothers* followed a long line of cases rejecting the patentability of both products of nature and insubstantial variations on previously known substances. If *Parke-Davis* was not very widely followed by other courts before the *Funk Brothers* decision, it certainly was not followed afterward. *See generally* Demaine & Fellmeth, *supra*, at 334-45 (recounting the history of case law dealing with patents on purified products of nature).

However, with the adoption of the 1952 Patent Act, the tide soon turned, and the *Parke-Davis* reasoning began to dominate federal jurisprudence. Appellate courts began approving patents on purified products of nature, justifying the patent by the technical differences between the product of nature and increased therapeutic or commercial value of the purified substance. *See generally* Demaine & Fellmeth, *supra*, at 349-60. It is not entirely clear why lower courts began departing from this Court's precedents after the adoption of the Act. One possible reason, supported by the fact that most such decisions related to pharmaceutical and biochemical patents, is that courts considered improvements in the field of health and medicine more urgent than in other fields having less direct and immediate effect on human welfare. They may have believed that a looser patent policy would be helpful to foster medical advances and reinterpreted the law accordingly.

Another possibility is that courts read the language of the new Patent Act as signalling a congressional desire to abandon or minimize the prohibition on patenting products of nature, because the Act included no such prohibition *expressis verbis*. On this theory, Section 103 of the Act forbade patents on variants of prior art (defined in Section 102 of the Act, 35 U.S.C. § 102) that would have been obvious at the time of invention. *See* 35 U.S.C. § 103. But Section 102 of the Act does not include undiscovered products of nature in its catalog of prior art. *Ergo*, the courts may have reasoned, obvious variants on undiscovered products of nature may be patented under the Patent Act. In short, "the Act seems to sanction by omission the patenting of obvious derivatives of naturally occurring phenomena." Demaine & Fellmeth, *supra*, at 383. If this hypothesis is correct, then these courts must have been unaware of, or must have ignored that, undiscovered products of nature do in fact qualify as prior art under the Patent Act. All human DNA is already in public use in this country, 35 U.S.C. § 102(a), by all persons whose body use that DNA biologically. Moreover, the courts improperly interpreted the codification of the scattered patent statutes as repudiating Supreme Court and CCPA precedents prohibiting patents on insignificantly altered products of nature.

Whatever the reason for this departure from this Court's precedents, the *Parke-Davis* reasoning gained ascendancy when the Court of Customs and Patent Appeals endorsed it in In re *Bergstrom*, 427 F.2d 1394 (C.C.P.A. 1970). There, the CCPA rejected the "consistent principle . . . that a claim to a purified material cannot be allowed unless the purified material exhibits properties and utilities not possessed by the unpurified material." *Id.* at 1398. Instead, the court relied on the tautology that, if the applicant sought a patent on a product of nature purer than its natural form, the applicant was not seeking to patent a product of nature in the first place. *Id.* at 1401-02. The Federal Circuit endorsed this line of reasoning in *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1206-07 (Fed. Cir. 1991), *cert. denied sub nom. Genetics Institute v. Amgen, Inc.*, 502 U.S. 856 (1991), and this new doctrine has represented federal jurisprudence ever since, though never endorsed by this Court.

The Federal Circuit's decision below follows and ratifies the *Parke-Davis* and *Amgen v. Chugai* line cases, mistaking the mere fact of human intervention using some knowledge, skill, or effort for the functionally inconsequential removal of natural DNA from its surroundings, as a basis for denying the status of a human gene as a product of nature. These are not, have never been, and should not be, the proper criteria for determining whether a product of nature has been transformed into patentable subject matter under this Court's jurisprudence.

Nonetheless, because of the Federal Circuit's current policy, the effective rule in practice is currently that a product of nature constitutes patentable subject matter as long as it has been somehow altered, no matter how trivially, by human intervention, giving it a superior practical use—typically a therapeutic, diagnostic, or research use—it did not have in its natural, unaltered state. This has allowed many patent applicants to successfully claim products of nature by merely qualifying the claims with the talismanic words "isolated," "purified," or "synthesized." *See* Demaine & Fellmeth, *supra*, at 358-59; Conley & Makowski, *supra*, at 394. Patent lawyers in the past three decades have openly used this formula to monopolize any commercial use of human genes. For example, one patent prosecutor advised fellow practitioners: "The discovery of a product in nature, although not an invention, may well lead to an invention *by the proper use of claim language*." Karl Bozicevic, *Distinguishing "Products of Nature" from Products Derived from Nature*, 69 J. PAT. & TRADEMARK OFF. SOC'Y 415, 426 (1987) (emphasis added). Notice that he said not "by inventive activity," but by the phrasing of the patent application. While patent prosecutors may celebrate the triumph of semantics over substance, it is bad law and bad policy. "Because the distinction between a statutory invention and a nonstatutory product of nature is one of substance rather than form, cases should not be resolved on the basis of incantations. . . . The case law simply does not support the existence of linguistic safe harbors." Conley & Makowski, *supra*, at 392.

The reasoning of these decisions leads to potentially absurd results by *reductio ad absurdum*:

> If any naturally occurring substance that cannot be found in purified form in nature were patentable the first time it was isolated and purified, then the first person to purify water could have patented it; the first person to strain blood cells out of blood could have patented pure plasma because plasma always contains blood cells in its natural state; and for that matter, the first person to climb up a banana tree, pull down a fruit, and peel it would have merited a patent on "isolated and purified" banana fruit, because in nature bananas always grow on trees and with peels.

Demaine & Fellmeth, *supra*, at 391.

As this Court recognized in *Mayo Collaborative Services v. Prometheus Laboratories*, 132 S.Ct. 1289, 1293 (2012), ultimately, all inventions are traceable back to products of nature and natural phenomena, which supply the particles, atoms and laws that make up all matter in the universe and allow it to interact. This Court has not had occasion to formulate a precise test for distinguishing products of nature from patentable inventions based on them, but it has clearly indicated factors that should be considered in the analysis.

Specifically, this Court rejected a patent on a natural citrus fruit treated with borax to resist mold on the ground that the resulting fruit had no "new or distinctive form, quality, or property. . . . There is no change in the name, appearance, or general character of the fruit." *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1, 11-12 (1931). In *Funk Brothers v. Kalo Inoculant,* part of the Court's rationale for invalidating the patent was that the claimed combination of bacteria did not alter the utility of any one of the bacteria species: "No species acquires a different use." 333 U.S. 127, 131 (1948). The Court's opinion upholding the patent on a recombinant bacterium in *Chakrabarty*, relied heavily on the fact that the bacterium was "markedly different" from any naturally occurring bacterium, and had "a distinctive name, character [and] use." *Chakrabarty*, 447 U.S. at 309-10.

From these and other cases, Demaine and Fellmeth determined that the Court has been using a "substantial transformation test" similar to the one traditionally used in customs law for determining the country of origin of a good from one country subjected to processing steps in another. Under this test, a preexisting product or combination of products traditionally becomes a new and different article if subjected to processing steps that cause the precursors to lose their identities and become "a new article having a new name, character, and use." *United States v. Gibson-Thomsen*, 27 C.C.P.A. 267, 273 (1940).

Demaine and Fellmeth articulated and justified this test as consistent with this Court's precedent in determining whether a product of nature had been sufficiently altered to qualify as an invention. Demaine & Fellmeth, *supra*, at 393-407. As noted, the Federal Circuit seems to have accepted that this test is the appropriate one, but it misapplied the test on the facts before it. The character of a human protein-coding gene is a double-helical molecule composed of nucleotides arranged for the production of a specific protein. The biological "use" of a protein-coding gene is the production of a specific protein. The character and use of the gene in its natural state and in "isolated" DNA is precisely the same. It is not even marginally different; much less is it "markedly different."

The Court should uphold its previous decisions requiring a substantial transformation of a product of nature to qualify it as patentable subject matter. As Demaine and Fellmeth argued, in the context of a protein-coding gene, a substantial transformation does not occur unless the gene has been so altered as to acquire a new and different biological function, which means producing something other than the protein for which the natural gene codes. *See id.* No other alteration to a natural biochemical is sufficient to avoid conferring a monopoly on all meaningful uses of the product of nature. *See id.*

The substantial transformation test articulated by this Court, as interpreted by Demaine and Fellmeth, fulfills the policy purposes of the patent law. It is clear in application, because only changes to a gene sequence that result in a new, synthetic protein would qualify as patentable subject matter. In other words, it draws a bright line between merely applying an idea taken from nature to a practical context (i.e., discovering a law of nature and "applying it") and creating something meaningfully different and man-made, an "invention." It is consistent with this Court's precedents, discussed above, because any change to the gene's biological function necessarily and markedly changes the gene's character and use. In contrast, an alteration that does not change the gene's biological function but merely uses it in a different context or adjusts the rate of expression would not qualify, because no invention has occurred with respect to that gene.[4] As Demaine and Fellmeth concluded:

> Transformation of biological function is not the same as change of context. For example, if a natural protein is discovered to promote cell growth in nature, the fact that the protein is only useful for therapeutic purposes after being purified, concentrated, or otherwise modified does not by itself render the modified protein "new." This is merely a change of context, not a transformation of biological function. If the protein's function is the same in the therapeutic context (e.g., promoting cell

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[4] For example, isolating the gene from the chromosome and using in an assay, or transfecting a vector with a clone of a natural gene to create a cell line would not qualify as a substantial transformation. The artificial cell line itself or the process of creating it could, however, qualify as patentable subject matter, because the biological function of the cells will have been altered by causing them to produce unnatural proteins.

> growth) as its function in nature, then no change of utility has occurred, and merely adjusting the form of the substance cannot work a substantial transformation on it. The same analysis applies to DNA molecules. If a naturally occurring DNA molecule has the useful function of coding for Protein X, then no purified or otherwise altered version of that DNA molecule can be "new" unless its claimed function is fundamentally different than coding for Protein X. Without a change in biological function, the DNA molecule lacks adequate creative input to qualify as an invention; it is little more than a molecule found in nature with superficial modifications.

Demaine & Fellmeth, *supra*, at 400.

The test also fits well with other key patent doctrines, such as the prohibition on patenting obvious innovations, 35 U.S.C. § 103, and the Doctrine of Equivalents. Section 103 of the Patent Act is the statutory codification of key federal jurisprudence defining "invention." As noted, merely extracting or reproducing a portion of a natural DNA molecule is not an invention, and the act of isolating human genes and cloning them is always obvious based on prior art. The Doctrine of Equivalents, as articulated by this Court, allows a patent owner to seek protection against nonliteral infringement of the claims when the accused product performs substantially the same function in substantially the same way to achieve the same result. *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 608 (1950).

A man-made gene that does not perform the same biological function as a natural gene would pass these tests and qualify as nonobvious and nonequivalent. If a product of nature is not patentable subject matter, neither should be an obvious modification of the natural product. The substantial transformation test achieves this outcome without discouraging meaningful technological advances. *See generally* Demaine & Fellmeth, *supra*, at 406 (discussing the advantages of the test).

Finally, because the U.S. Court of Appeals for the Federal already interprets the substantial transformation test in the customs law context, the test will already be familiar to it.

When the law is uncertain, courts should consider whether the policy consequences of one interpretation or another serves the legislative purpose. As noted, the Constitution does not authorize Congress to grant patents to encourage all knowledge of any kind whatsoever, but only to encourage "Discoveries." U.S. CONST. Art. I, sec. 8, cl. 8. The Patent Act, too, authorizes patents only for those who "invent" a new and useful product. 35 U.S.C. § 101. Judge Lourie claimed that his interpretation of the Patent Act serves the patent law's policy purposes by encouraging innovation, *Association for Molecular Pathology*, 689 F.3d at 1331, while in the same breath insisting that "it is ultimately for Congress" to weigh the policy consequences of overturning the case law holding human DNA patentable, *id.* at 1330-31. This is a rather disingenuous self-contradiction. In any case, Congress has never blessed the patenting of human genes; it was lower courts themselves that engaged in their own act of invention to create a policy of allowing patents on human genes, in defiance of this Court's precedents disapproving of patents on very similar purified products of nature. To claim that it is Congress, not the courts, that should reverse lower court decisions usurping Supreme Court precedents is absurd. Despite considerable industry lobbying in favor of allowing gene patents and public sentiment opposed to such patents, Congress has chosen not to legislate on the subject. It clearly prefers to leave this issue to the courts.

Using the substantial transformation test, as advocated here, serves the purposes of patent law. It encourages technological innovation beyond mere copying of human genes without imposing excessive tollbooth costs on biotechnology research. It avoids at least three negative repercussions that would seriously undermine the public policies promoted by the Patent Act.

First, allowing patents on isolated human genes over-rewards the *least* difficult, costly, and inventive stage of the development process of pharmaceuticals, assays, and other downstream therapeutic inventions. An efficient patent system would grant patents conferring a scope of protection no greater than what was invented—an observation made by Jeremy Bentham two hundred years ago. 2 JEREMY BENTHAM, THE

RATIONALE OF REWARD ch. IX (1825). By awarding patents conferring a legal monopoly on exceedingly broad and largely unknown downstream medical research uses of the gene, gene patents awards a windfall on upstream researchers of basic biology while creating barriers to the more difficult and exacting research closer to therapeutic end-uses.

Second, unlike the great majority of inventions, it is exceedingly difficult to "invent around" human genes for, by way of example, ascertaining a patient's susceptibility to gene-linked disorders or creating biologically necessary human proteins. Isolating natural genes or reproducing them, or their coding regions, is the only efficient and predictable method of making natural genes scientifically and commercially available on a large scale. Demaine & Fellmeth, *supra*, at 418. Allowing patents on isolated human genes gives the first person to sequence the gene an effective exclusionary right not just to that gene itself, but to the protein it produces and all uses of the gene in any later medical invention, including cell lines for the production of the protein, assays to detect the presence of the gene in medical patients, and any other use later discovered.[5]

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[5] Patents on "isolated and purified" natural human proteins have also been sanctioned by the Federal Circuit, and are even more problematic than the patenting of human genes. It is at least theoretically possible to produce pharmaceutically viable human proteins through methods other than recombinant technology, such as pure chemical protein synthesis. A patent on a human protein by the

Third, because of the difficulty of inventing around basic building blocks of nature and the fact that multiple genes may be involved in any given medical condition, there is a risk of creating an "anticommons" by which the owner of any one human gene patent can hold up or block the development of important medical diagnostics and therapies, and in any case would raise the costs of basic medical research through higher license search costs and stacking of license fees on top of each other. Monopolization of products of nature "through the grant of a patent might tend to impede innovation more than it would tend to promote it." *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289, 1293 (2012); *see* Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCI. 698 (1998). Far from promoting the progress of scientific innovation, such patents tend to retard progress, as the empirical

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first person to express it through a vector transfected with the cDNA clone of a human gene monopolizes a constituent element of the human body even though someone else may be able to develop an entirely different and nonobvious method for synthesizing that protein chemically. *See* Aaron Xavier Fellmeth, *The Challenge to Patent Law of Pure Chemical Protein Synthesis*, 23 NATURE BIOTECH. 547 (2005). By adopting the substantial transformation test proposed here with regard to all natural biochemicals, this Court reaffirm the invalidity of such "gold rush" tactics that attempt to monopolize products of nature found but not invented by the patent applicant.

evidence suggests it has already done. *See* Julia Carbone et al., *DNA Patents and Diagnostics: Not a Pretty Picture*, 28 NATURE BIOTECH. 784 (2010); Michelle R. Henry et al., *DNA Patenting and Licensing*, 297 SCI. 1279 (2002); Mildred K. Cho et al., *Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services*, 5 J. MOLECULAR DIAGNOSTICS 3 (2003); Robert Cook-Deegan & Chistropher Heaney, *Patents in Genomics and Human Genetics*, 11 ANN. REV. OF GENOMICS & HUM. GENETICS 383 (2010); Kurt Eichenwald, *Push for Royalties Threatens Use of Down Syndrome Test*, N.Y. TIMES, May 23, 1997, at A1.

In short, patents on "isolated and purified" human genes are not just bad law, they are bad public policy. The Court should reaffirm its long-held jurisprudence denying the patentability of insignificantly altered products of nature. It should specifically approve a substantial transformation test to weed out patents on biologically identical derivatives of human genes and other natural biochemicals.

III. cDNA sequences copying human DNA are products of nature unless substantially transformed into a new product with a different biological function.

Some of the claims in this case, such as claim 2, involve complementary DNA (cDNA) rather than "isolated" human DNA. cDNA corresponds to the portion of the natural DNA sequence that codes for a protein (exons). By omitting the non-coding regions of the gene (introns, typically comprising up to 30% of the sequence), scientists may create a cDNA molecule that they can later transfect into a vector (i.e., a host cell) for regulated expression of the protein, which can be used as a living protein factory for the production of pharmaceuticals or for the screening of drug candidates that are intended to act on the protein to resolve a disorder.

This Court should treat a cDNA molecule having the same nucleotide sequence as the coding region of a natural gene no differently from that gene itself. If a human gene is product of nature, so too is its coding region, and by extension a copy through cDNA or otherwise of the gene's coding region. The coding region is as much a product of nature as the DNA molecule as a whole. It is, indeed, its essence. "[D]espite its nominal chemical distinctiveness, [cDNA derived from a human gene] is functionally indistinguishable from natural DNA and RNA. It contains exactly the same genetic information as its natural counterpart. It can do precisely the same work as a naturally occurring gene—protein synthesis—and it employs precisely the same processes to do it, whether in the body or in the laboratory." Conley and Makowski, *supra*, at 394. A cDNA copy of a human gene has precisely the same function—to express a specific protein—that the gene has in its natural state. "The geneticist who discovers that a particular sequence produces a particular protein and isolates that sequence no more creates the protein-producing nature of the sequence than the *Funk*

Brothers Seed patentee created the noninhibitory nature of the *Rhizobium* bacteria." Demaine & Fellmeth, *supra*, at 409.

The U.S. government argued below that cDNA copies of human DNA are patentable subject matter if they pass a "magic microscope test," meaning that nowhere in the human body can a cDNA sequence be found as such. *Association for Molecular Pathology*, 689 F.3d at 1326. In effect, the government proposed a new test, under which a DNA molecule copied literally from the chromosome is a product of nature, while a molecule such as cDNA, which copies the most important part of the natural DNA molecule, is patentable subject matter, because the cDNA molecule is not found in nature in that precise form.

The government's attempt to distinguish a product merely extracted from nature (an "isolated" natural gene) from a product extracted from an extract of nature (the exon sequence of a natural gene) is a distinction without a difference. cDNA may be one step removed from the natural gene (its introns are not copied), but it is a simple step to accomplish and is equivalent for all biological purposes. As Judge Lourie correctly observed below, isolated genes are also not found *as such* in nature. This Court should reject the government's proposed distinction between products of nature and inventions. Exact identity to the product of nature is not the appropriate test for determining patentable subject matter. The Court should not sanction the patenting of *any* biologically insignificant alteration of a human gene without more, regardless of how much of the natural DNA sequence is omitted. A person claiming the cDNA sequence of a natural gene no more created that sequence than he created the gene itself.

Moreover, the argument that cDNA differs substantially from the natural gene ignores the role of messenger ribonucleic acid (mRNA) in gene expression. mRNA is a natural molecule that conveys information from the DNA to the ribosome during natural translation of coding DNA into proteins. Like a cDNA molecule, *the mRNA molecule contains only the coding region of the gene.* "The notion of removing introns, regions of a DNA sequence that do not code for proteins, is not a human invention. In fact, during the process of natural DNA transcription, an mRNA molecule is created as a copy of a gene in preparation for protein synthesis. During the creation of the mRNA, only the exons are reproduced." Demaine & Fellmeth, *supra*, at 408. The only significant difference between an mRNA molecule and its correlative cDNA molecule is that the former is single-stranded and the latter is double-stranded.[6] Scientists who create cDNA merely use well-known techniques for converting a natural mRNA molecule into cDNA. Indeed, *even this process happens naturally*; cells create processed pseudogenes in just this way. In fact, an important function of cDNA in biotechnology is to reproduce the natural mRNA so that it can be translated into the natural protein. The cDNA is a mere replica of natural mRNA and pseudogenes.

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[6] RNA also has a ribose sugar instead of deoxyribose sugar in its backbone and substitutes uracil for thymine in its base composition. These differences do not affect the amino acid sequence conveyed by the sequence of bases.

This Court should apply the substantial transformation test to find that cDNA versions of naturally occurring human genes, if they merely "isolate and purify" those genes by copying the non-coding regions, do not constitute patentable subject matter. As with merely "isolated" genes, the biological function of the cDNA is identical to that of the natural gene—the expression of a specific protein. Only if the cDNA is altered to perform protein expression in a "markedly different" way than the nature gene—generally by expressing an unnatural protein—should the cDNA be considered patentable subject matter.

CONCLUSION

For the foregoing reasons, the judgment below should be reversed.

Respectfully submitted,

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CURIAE
BRIEF

Supreme Court, U.S.
FILED
MAR 4 2013
OFFICE OF THE CLERK

No. 12-398

IN THE
Supreme Court of the United States

ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,
Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,
Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR AMICI CURIAE GENENTECH, INC.; ROCHE MOLECULAR SYSTEMS, INC.; VENTANA MEDICAL SYSTEMS, INC.; ROCHE DIAGNOSTICS OPERATIONS, INC.; ROCHE DIAGNOSTICS CORPORATION; AND HOFFMANN-LA ROCHE INC. IN SUPPORT OF RESPONDENTS

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IN THE

Supreme Court of the United States

No. 12-398

ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,
Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,
Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR AMICI CURIAE GENENTECH, INC.; ROCHE MOLECULAR SYSTEMS, INC.; VENTANA MEDICAL SYSTEMS, INC.; ROCHE DIAGNOSTICS OPERATIONS, INC.; ROCHE DIAGNOSTICS CORPORATION; AND HOFFMANN-LA ROCHE INC. IN SUPPORT OF RESPONDENTS

INTEREST OF AMICI CURIAE[1]

Amici curiae are biotechnology and biopharmaceutical companies with a long history of industry leadership in research and development of therapeutic and diagnostic applications of recombinant DNA technology. Amici rely on patent protection to finance and develop these technologies, which have saved countless lives and which promise even greater future benefits.

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[1] No counsel for a party authored this brief in whole or in part, and no persons or entities, other than amici or their counsel, made a monetary contribution to the preparation or submission of this brief. Letters consenting to the filing of this brief are on file with the Clerk of the Court.

Amici are all members of the Roche Group ("Roche"), a corporate family comprising innovative, research-oriented healthcare groups across the globe. Roche is the world's largest biotechnology company. It divides its operations into two core businesses—pharmaceuticals and diagnostics—both of which rely heavily on investment in and use of recombinant DNA technologies. Close cooperation between Roche's pharmaceutical and diagnostic divisions enables the company to tailor treatments to specific patient subpopulations based on the latest scientific understanding of biology and disease at the molecular level. Roche has been at the forefront of the development and commercial application of these technologies since their inception.

Genentech is a leading biotechnology company that uses human genetic information to discover, develop, manufacture, and market human pharmaceuticals for significant unmet medical needs, especially in the areas of oncology, immunology, neuroscience, metabolism, and infectious disease. In the early 1970s, Genentech's founders pioneered the use of recombinant DNA technology to develop products with practical applications. Genentech has an extensive track record in all phases of bringing new disease treatments to patients—from discovery research through clinical development, manufacturing, and commercialization.

Roche Molecular Systems develops, manufactures, and supplies a wide array of innovative medical diagnostic products, services, tests, platforms, and technologies. Many of these products use the company's Nobel Prize-winning polymerase chain reaction technology to detect genetic material from cancerous cells and infecting pathogens, such as HIV or hepatitis. Because the tests are capable of identifying and characterizing disease earlier and more specifically than tests based on the body's immune response, patients can be treated and monitored with great precision.

Roche Diagnostics offers a broad portfolio of tools that help healthcare providers in the prevention, diagnosis, and management of diseases like HPV, HIV, heart failure, and diabetes, as well as other medical conditions, such as infertility and blood coagulation. These products and services are used by researchers, physicians, patients, hospitals, and laboratories worldwide to help improve people's lives.

Ventana Medical Systems is an innovator in the field of tissue-based diagnostic solutions. The company discovers, develops, and delivers medical diagnostic systems and biopsy-based cancer tests that are shaping the future of healthcare. Ventana is the leading supplier of cancer diagnostic systems to the pathology market, manufacturing over 220 cancer tests with related instruments for four million people afflicted with cancer yearly around the world.

The development of both diagnostic and therapeutic applications of recombinant DNA technologies is capital intensive and time consuming. Success in these fields could not be achieved without the protections and incentives provided by the patent system. Uncertainty regarding the patent eligibility of isolated DNA molecules would jeopardize current and future innovation in these fields. The question presented in this case is thus of great significance to amici.

SUMMARY OF ARGUMENT

Biotechnology companies use modern DNA technologies to identify, characterize, and treat disease. Through a combination of diagnostic and therapeutic tools, the industry has provided physicians and patients with effective products to detect, monitor, and treat a wide range of debilitating diseases. In many instances, the diagnostic or therapeutic tool is a synthetically created protein or nucleic acid product that is intended to resemble, at least in some respects, natural compositions of the body. Biotechnology companies can only make and justify the enormous investment necessary to develop these types of products if they can be assured that patent protection will allow them a return on their investments.

Petitioner proposes denying patent protection to any isolated "product of nature," a category that he defines exceptionally broadly. Such an expansive rule could threaten the patentability of a vast array of biotechnology products that, although they may contain some analogue of a substance found in nature, are engineered in a lab through complex scientific processes and are manufactured by scientists, not by nature. This Court should proceed with extreme caution and should consider the impact of any potential decision not only on the case before it or fanciful hypotheticals like the patenting of leaves or gold but also on the many groundbreaking innovations in biotechnology that could be affected.

The dangers and difficulties of a broad "product of nature" exception are illustrated by three examples of technologies from amici's own portfolio: (1) recombinant therapeutic proteins; (2) monoclonal antibodies; and (3) DNA-based diagnostic tests. All of these technologies have or might have analogues in nature, but they are all decidedly the product of human ingenuity and deserving of patent protection. Mindful of the law of unintended consequences, the Court should ensure that its ruling in this case does not imperil the patent protection relied on by innovators for financing and developing these inventions.

ARGUMENT

As the Court observed only last Term, "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas." *Mayo Collaborative Servs.* v. *Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1293 (2012). That is equally true of discoveries in biotechnology, most of which harness natural principles or build on structures found in nature. The sweeping "product of nature" exception to patent eligibility that petitioner seeks could create tremendous uncertainty for the biotechnology industry if the Court were to adopt it. The purpose of this brief is to educate the Court about the broad range of biotechnology inventions beyond the single invention at issue in this case, the complex questions that could arise if the Court adopts petitioner's position, and the need to ensure that the Court does not sweep too broadly.

I. AMICI AND OTHERS IN THE BIOTECHNOLOGY INDUSTRY HARNESS HUMAN INGENUITY TO DEVELOP PRODUCTS THAT ADDRESS UNMET MEDICAL NEEDS

A. Recombinant Technology That Utilizes Isolated DNA Has A Wide Range Of Therapeutic And Diagnostic Uses

1. Recombinant proteins are synthetic products made in a laboratory through complex techniques that are intended to create a product closely resembling molecules found in nature, including in the human body. Armed with these techniques, biotechnology has played an increasingly important role over the last several decades both in the elucidation of the molecular causes of disease and in the development of new diagnostic methods and better targeted drugs. The modern biotechnology industry emerged in the 1970s and took off after this Court's decision in *Diamond* v. *Chakrabarty*, which held a bacterium to be patent eligible as a "manufacture or composition of matter—a product of human ingenuity 'having a distinctive name, character [and] use.'" 447 U.S. 303, 309-310 (1980). Since then, the industry has created hundreds of new therapies, drug products, and vaccines.

Amici were among the pioneers of the use of recombinant techniques to create products to treat disease. This unique approach uses proteins as therapeutic drugs, rather than the smaller chemicals of traditional pharmaceuticals. One way to create such a protein is to create a cDNA molecule that codes for a particular protein and then use controlled laboratory conditions to produce that protein outside the human body. *See, e.g.*, Holman, *The Impact of Human Gene Patents on Innovation and Access*, 76 UKMC L. Rev. 295, 324-325 (2007). Through this technique, living cells—such as bacteria or more complex mammalian cells—serve as mini-factories to manufacture the appropriate proteins. Although produced in a lab, the finished proteins closely resemble molecules found in the human body.

The first medicine to be produced in this way was human insulin, which is used to treat diabetes. By developing a technique to produce human insulin in bacterial cells, Genentech replaced the traditional process of extracting insulin from the pancreatic glands of pigs and cows. *See* Roche, *Biotechnology: New Directions in Medicine* 11-13 (3d ed. 2008); National Research Council, *Reaping the Benefits of Genomic and Proteomic Research* 47-48 (2006). Some 200 million diabetics worldwide now benefit from the development and production of human insulin. *See Biotechnology* 12.

Recombinant therapeutic proteins like human insulin have increased dramatically in number and frequency of use in recent years, providing patients with effective products to treat a wide range of debilitating diseases such as cancer, arthritis, and macular degeneration, and are in development for other unmet medical needs, such as Alzheimer's disease.

2. Biotechnology companies also use recombinant technologies to create diagnostic tests to identify patients predisposed to a given disease, to conclusively diagnose disease or differentiate disease subtypes and prognosis, to monitor treatment efficacy, and to ensure the safety of the blood supply. Before these innovations, clinicians were often forced to rely on tests that could take weeks to produce conclusive results. Earlier detection of disease can mean earlier and more effective treatment.

Many of these innovative diagnostic tests are based on Roche's Nobel Prize-winning polymerase chain reaction (PCR) technology. *See Biotechnology* 58-59. PCR is a technique for "produc[ing] enormous numbers of copies of a specified DNA sequence." Watson *et al.*, *Recombinant DNA* 79 (2d ed. 1992) (emphasis omitted). PCR involves repeated cycles of heating and cooling during three key steps. First, double-stranded DNA containing the target DNA sequence is heated until it denatures into single strands. Second, the mixture is cooled to allow "primers" to bind to each of the strands. A primer is a short single-stranded DNA molecule that is synthetically designed to be complementary to "sites that flank the target region, one on each strand." *Id.* at 81 fig.2. The primer marks out the starting points on each strand of the sequence to be copied. Third, the mixture is heated to the point at which the enzyme DNA polymerase begins synthesizing new complementary strands at the primer sites. The result is two double-stranded molecules—each consisting of one strand from the original DNA molecule and one strand synthesized by DNA polymerase—that contain the target region marked out by the primers. After more heating and cooling cycles, two copies become four, then eight, sixteen, and so forth, all synthetically created in the lab.

A more advanced form of PCR, called "real-time PCR," makes use of an additional short single-stranded DNA molecule that is designed to bind at the middle of the target DNA sequence. This "probe" is labeled to generate a signal when it binds, enabling even more specific and sensitive detection of a target sequence.

PCR thus allows scientists to take a specimen of genetic material, even from just one cell, and copy its genetic sequence over and over, generating a test sample with millions of copies. The primers and probes that make this technique possible are synthetically produced isolated DNA molecules.

3. These advances in DNA-based diagnostics and therapeutics are part of biotechnology's nascent personalized medicine revolution. The goal of personalized medicine is "tailor[ing] treatment to individual patients" based on advances in diagnostic testing for genomic variations. FDA, *Advancing Regulatory Science at FDA* 10 (2011); *see also* Personalized Medicine Coalition, *The Case for Personalized Medicine* 2 (3d ed. 2011) ("What is different about medicine today, and the reason the word 'personalized' has been added for emphasis, is that technology has brought us much closer to exquisite precision in disease diagnosis and treatment."). Personalized medicine recognizes that differences in the genome make each of us a unique individual—not only in appearance and behavior, but also in terms of our health risks and response to treatments. These differences offer key insights to help in finding the right treatment for each individual.

Amici are at the forefront of this new field, which bridges both therapeutic and diagnostic applications of recombinant DNA technologies. For example, every drug being developed by amici now has a biomarker program associated with it, meaning that measurable biological indicators are studied to evaluate whether the drug is indicated for a given patient and to monitor the drug's therapeutic efficacy. This type of personalized medicine has become a priority healthcare issue at the highest levels of government. The FDA has increasingly required the use of "companion diagnostic[s]" as a condition of approving therapeutic products. *See* FDA, *Draft Guidance for Industry and Food and Drug Administration Staff—In Vitro Companion Diagnostic Devices* 6-7 (2011). Obtaining FDA approval of such companion diagnostics requires rigorous validation techniques and a substantial investment of resources.

B. Biotechnology Innovation Depends On A Stable Patent System To Fund The Research, Development, And Commercialization Of These New Technologies

Biotechnology companies such as amici invest substantial sums of private capital to make these innovations possible. While advances in scientific knowledge are leading to dramatic improvements in identifying biological targets to fight many diseases, the complexity of research is rising significantly. Bringing a single biotechnology product to market, including basic research, clinical trials, and post-approval testing, now takes up to 12 years and costs on average $1.6 billion. Roche, *Annual Report 2012*, at 25 (2013); Grabowski, *Follow-on Biologics*, 7 Nature Revs. Drug Discovery 479, 482 fig.2 (2008).

This type of private investment depends on a stable patent system that rewards innovation and risk-taking. Biotechnology companies can only make and justify the enormous investment necessary to develop new products if they can be assured that patent protection will allow them a return on their investments. *See, e.g.*, Toneguzzo, *Impact of Gene Patents on the Development of Molecular Diagnostics*, 5 Expert Op. Med. Diagnostics 273, 274 (2011) ("industry has consistently confirmed that the protection that a patent affords is a key consideration for making an investment" in molecular diagnostic development); *id.* ("without a patent investment is not made and technology is not developed"). Patents are critical to reassuring investors that they will earn a reasonable financial return on products that make it to market. *See* Barfield & Calfee, *Biotechnology and the Patent System* 27-28 (2007).

The future of the biotechnology industry "depends on the continued support that patent exclusivity facilitates through the incentive to invent and the incentive to invest in innovation." Sung, *Medical Alert: Alarming Challenges Facing Medical Technology Innovation*, 6 J. Bus. & Tech. L. 35, 58 (2011). Indeed, uncertainty over the patentability of biotechnology products has in the past had dramatic negative effects on the industry. *See* Davies, *Cracking the Genome* 205 (2001) (explaining that after President Bill Clinton and Prime Minister Tony Blair issued a statement implying that human DNA would not receive patent protection, "the markets panicked, sending the technology sector of the U.S. stock market into a tailspin"). Similar uncertainty following this Court's decision in *Mayo* may have contributed to the decrease of 15 percent in investment dollars in the industry in 2012. *See* Press Release, PricewaterhouseCoopers & National Venture Capital Association, *Annual Venture Investment Dollars Decline For First Time In Three Years* (Jan. 18, 2013); *see also* Thomas, Cong. Research Serv., R42815, Mayo v. Prometheus*: Implications for Patents, Biotechnology, and Personalized Medicine* 3 (2012) ("VC firms must carefully weigh the economic value of a company's patent portfolio in determining whether to make an investment, and the security of intellectual property is a key component in this analysis."). The Court should be careful not to upset reliance interests or to create uncertainty that will chill future innovation and potentially cripple this vital industry.

II. MANY THERAPEUTIC AND DIAGNOSTIC APPLICATIONS OF BIOTECHNOLOGY RESEMBLE COMPOUNDS FOUND IN NATURE ONLY BECAUSE HUMAN INGENUITY ACHIEVED THIS CONGRUENCE

Petitioner urges the Court to create a general "product of nature" exception broad enough to deny patent protection to many isolated nucleic acids and proteins. But, as the examples below illustrate, petitioner's argument is flawed in multiple respects and could have serious unintended consequences.

First, petitioner's argument underestimates the role of human ingenuity in creating isolated molecules that have new utilities beyond anything that exists in nature. Although many of these molecules are claimed in isolated form to differentiate them from any naturally occurring analogue, it would be a mistake to assume that this means they are simply extracted from nature like gold from a mine. More typically, the isolated form of a molecule is created in a laboratory or a factory. The isolated molecule often becomes useful therapeutically or diagnostically only when it can be synthetically created by humans rather than nature.

Second, the fact that the compositions of matter created through recombinant processes and other techniques resemble naturally occurring analogues does not detract from the inventive nature of these products. In many instances, genetically engineering proteins that are similar to those that the human body might produce is a chief design goal, achievable only at great expense and difficulty. Because these proteins are, by design, similar to what occurs in nature, it is easy to fall into the trap of equating them with natural molecules. But as the examples below illustrate, their very similarity is a product of human ingenuity.

Third, even when there is no known naturally occurring analogue to a molecule at the time of invention and patenting, a broad product of nature exception would create a cloud of uncertainty because there is always a risk that a comparable molecule might later be found to exist in nature. In fact, patent challengers would have a strong incentive to seek out such evidence, much in the way that petitioner has tried to find examples of DNA or cDNA that he claims is "isolated" within the body.

Fourth, it is important not to lose sight of the basic bargain at the heart of the patent system. The full cycle of patent protection moves from the incentive to invent and disclose, through a limited period of market rewards, to the end point of every patent—its expiration and the enrichment of the public domain.

A. Past Therapeutic Breakthroughs Using Recombinant DNA Were Made Possible By The Patent Eligibility Of Isolated DNA

Recombinant techniques and isolated DNA molecules have played a central role in therapeutic advances achieved by amici. These advances are well illustrated by Genentech's path-breaking synthesis in the 1980s of two proteins found in human blood: tissue-type plasminogen activator (t-PA) and Factor VIII. The patent system was integral to fueling the development and commercialization of these lifesaving therapeutics, which have now been used to treat hundreds of thousands of patients. The possibility of patent protection spurred investment in research and development, and the security of a patent encouraged researchers to disclose their discoveries. Yet, because the products Genentech created through recombinant technology resemble proteins found in the human body—and indeed are therapeutically useful for that very reason—petitioner's broad rule would have created substantial uncertainty that could have chilled these advances.

1. t-PA is a protein that plays a role in the process of dissolving blood clots, which are helpful in staunching bleeding but which can also clog blood vessels and cause heart attacks and strokes. Blood clots are formed in part by a fibrous protein called fibrin. *See* Colman *et al.*, *Overview of Hemostasis*, *in Hemostasis and Thrombosis* 3, 11-14 (5th ed. 2006). t-PA catalyzes the conversion of another protein (plasminogen) into an enzymatically active form (plasmin) that dissolves the fibrin in a blood clot.

Genentech's interest in synthesizing t-PA was sparked by Belgian chemist Désiré Collen and colleagues, who in 1978 reported a key conceptual insight into the function of the protein: It is much more active in catalyzing the conversion of plasminogen into plasmin when fibrin is present—such as at the site of a blood clot—than when fibrin is not present. *See* Wiman & Collen, *Molecular Mechanism of Physiological Fibrinolysis*, 272 Nature 549, 549-550 (1978). By contrast, prior to Genentech's innovation, the only available therapeutic plasminogen activators were not fibrin specific. *See* Pennica *et al.*, *Cloning and Expression of Human Tissue-Type Plasminogen Activator cDNA in* E. Coli, 301 Nature 214, 214 (1983). When given to patients, the plasminogen activators available at the time caused systemic activation of plasminogen—not merely activation near the blood clot—which was inefficient and risked causing hemorrhaging. *Id.* Although it appeared that t-PA would be a superior treatment to dissolve blood clots in heart attack and stroke victims, at the time there was no way to produce t-PA in therapeutically useful quantities.

Genentech and Collen collaborated on a project to synthesize t-PA. After almost three years of work, the Genentech team successfully mapped and isolated the DNA coding for human t-PA. *See* Pennica *et al.*, 301 Nature at 217 fig.3B. The first step was to isolate the messenger RNA (mRNA) present in a line of melanoma cells known to produce human t-PA in significant quantities. *Id.* at 215. The mRNA thought to express t-PA was identified by sorting mRNA samples according to size, translating size-selected samples into polypeptides, and observing which polypeptides would bind with an antibody specific to t-PA. *Id.* The most promising pool of size-sorted mRNA was then used to prepare a library of cDNA. The team designed a labeled nucleic acid sequence based on the amino acid sequence of a short fragment of the t-PA protein and used the nucleic acid "probe" to search the cDNA library for cDNAs that encoded the t-PA protein fragment. *Id.* at 215-216. The team succeeded in identifying a single promising candidate, a 2,304 base pair cDNA fragment that the team knew could not be the complete code because it did not express the terminal sequence of the t-PA molecule. *Id.* at 216. A second cDNA library was created and successfully probed to identify the remainder of the cDNA that encodes t-PA. *Id.* at 216-219.

Genentech promptly disclosed this discovery in a patent application. *See* U.S. Patent No. 4,766,075 col. 30, ll. 67-68 (claiming the "DNA isolate consisting essentially of a DNA sequence encoding human tissue plasminogen activator"). The patent claims a "DNA isolate," but recombinant t-PA was not isolated in any conventional sense. It was synthetically constructed, over several years and at significant expense, through careful construction and probing of bacterial libraries of cDNA fragments, then combining portions of the cDNA fragments to create the full cDNA.

2. Genentech's invention of recombinant Factor VIII followed a similar pattern. Factor VIII is a protein that plays an essential role in blood clotting. In the human body, Factor VIII is secreted into the bloodstream by certain cells found in the liver, kidneys, spleen, and lymph nodes. Kaufman *et al.*, *Factor VIII and Hemophilia A, in Hemostasis and Thrombosis* 151, 153. The protein is missing or inactive in persons with Hemophilia A, a condition that can be marked by spontaneous and uncontrolled internal bleeding. *See* Wood *et al.*, *Expression of Active Human Factor VIII from Recombinant DNA Clones*, 312 Nature 330, 330-331 (1984). If proper measures are not taken promptly, the bleeding can cause crippling deformities or even death. More than 130,000 people around the world suffer from this type of Factor VIII deficiency. World Federation of Hemophilia, *Annual Global Survey 2011*, at 3 (2012).

In 1981, a team of Genentech scientists began research into producing human Factor VIII through recombinant technology. "[T]he plight of hemophiliacs was the crucial driving force" behind researchers' development of synthetic human Factor VIII. Gitschier, *Remembrances of Factor VIII*, 2 J. Thrombosis & Haemostasis 383, 383 (2004). Prior to Genentech's development of the recombinant method for producing human Factor VIII, hemophiliacs were treated with Factor VIII concentrates, which were purified from human blood plasma. Because Factor VIII occurs naturally in only minute quantities in blood, it was necessary to pool blood plasma from thousands of donors in order to produce the purified Factor VIII. *See id.*; Wood *et al.*, 312 Nature at 331. This method carried the risk that the treatment would transfer infectious agents such as HIV and hepatitis from the blood of a donor. *See id.*; Kaufman *et al.*, *Synthesis, Processing, and Secretion of Recombinant Human Factor VIII Expressed in Mammalian Cells*, 263 J. Biological Chem. 6352, 6352 (1988).

To address this unmet medical need, Genentech began by isolating and characterizing the region of the human X chromosome containing the complete Factor VIII gene. *See* Gitschier *et al.*, *Characterization of the Human Factor VIII Gene*, 312 Nature 326, 326 (1984). The Factor VIII protein is "four times as big" as t-PA, which made isolating its corresponding genomic DNA and cDNA "extremely difficult." Kleid, *Scientist and Patent Agent at Genentech* 161 (2002) (oral history). The Genentech team started by breaking the large protein into small pieces and then painstakingly determining the amino acid sequence of one of the small protein pieces. *See id.*; Gitschier, 2 J. Thrombosis & Haemostasis at 383-385; *see also Scripps Clinic & Research Found.* v. *Genentech, Inc.*, 666 F. Supp. 1379, 1382 (N.D. Cal. 1987). Based on the amino acid sequence of a short Factor VIII protein fragment, the team designed and constructed a radiolabeled nucleic acid probe, which was used to probe a large library of small pieces of human genomic DNA. A new labeled nucleic acid probe was then designed using sequences from the ends of this genomic DNA, and the library was screened again with the probe to identify "the next sequence downstream" along the Factor VIII sequence. Kleid 161; *see also* Wood *et al.*, 312 Nature at 332. By repeating this process, the Genentech team was able to piece together the entire sequence necessary to express Factor VIII. Kleid 161.

In 1984, Genentech disclosed this information in a patent application. Gitschier, 2 J. Thrombosis & Haemostasis at 387; *see* U.S. Patent No. 5,618,789 col. 41, ll. 1-2 (claiming "[r]ecombinant functional human factor VIII free of viral contaminants that affect humans").

3. t-PA and Factor VIII were not therapeutically useful until they could be manufactured in a laboratory, and they could not be manufactured in a laboratory until Genentech had synthetically constructed the cDNAs needed to express them. That breakthrough permitted the company to express the proteins in mammalian ovary cells. *See* Activase® (alteplase) Prescribing Information 1 (2011); Kleid 162; Gitschier, 2 J. Thrombosis & Haemostasis at 383-385. Once the proteins could be expressed in and harvested from mammalian cells, they were available in sufficient quantities to permit clinical trials and, ultimately, production of commercial therapeutics.

Recombinant t-PA is approved by the FDA to treat heart attacks, strokes, and pulmonary embolisms. *See* Activase® (alteplase) Prescribing Information 1. It is the only thrombolytic drug approved for the treatment of acute ischemic stroke, and it has been used to treat more than 240,000 patients in the United States alone. The public disclosure of Genentech's work on recombinant t-PA has prompted further downstream innovation, including the creation of synthetic variants of t-PA with utilities that are still being explored. *E.g.*, White & Van de Werf, *Thrombolysis for Acute Myocardial Infarction*, 97 Circulation 1632, 1641 (1998).

Genentech's development of a recombinant, virus-free version Factor VIII virtually eliminated the risk of transmitting human viruses when administering this protein. Recombinant Factor VIII has been approved since 1993 for the treatment of Hemophilia A. *See* Gitschier, 2 J. Thrombosis & Haemostasis at 383. Since then, the therapeutic has been instrumental in saving the lives of thousands of hemophiliacs.

4. Recombinant t-PA and Factor VIII are success stories not only for biotechnology but also for the patent system. The arc from unmet medical need to investment, discovery, disclosure, commercialization, and further innovation is exactly how the patent system is intended to work.

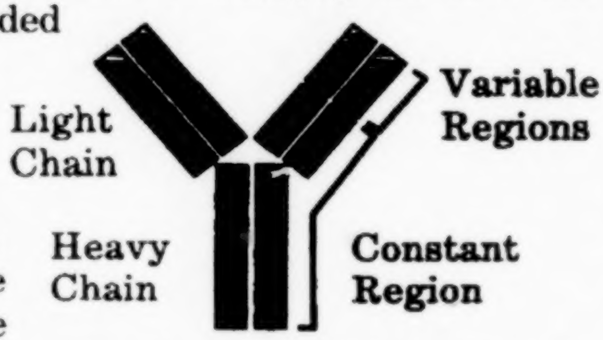
Uncertainty regarding the patent eligibility of the cDNA used to produce recombinant t-PA or Factor VIII or the recombinant proteins themselves could have significantly impeded these advances. The peril is particularly vivid for Factor VIII. It was patent protection for Factor VIII that permitted Genentech to license the rights to production and marketing of the protein in order to make the product available commercially quickly and efficiently. *See* Press Release, Genentech, *Cutter To Receive Factor VIII License from Genentech* (Sept. 11, 1984). Genentech also entered into cross-licensing agreements designed to allow multiple companies to "proceed with independent development of recombinant Factor VIII products, while avoiding potential disputes over competing patent positions." Press Release, Genentech, *Cross-Licensing Agreement Reached on Factor VIII Genetically Engineered Clotting Agent for Hemophiliacs* (Mar. 21, 1989). The limited period of exclusivity that the patent system provided made it economically viable for these companies to disclose their discoveries and to work together to make the products quickly available to patients in need.

B. Therapeutic Monoclonal Antibodies Are A Highly Promising Avenue Of Research That Would Be Imperiled By Petitioner's Broad Rule

Antibodies are another vivid example of the technologies that could be threatened by an overbroad "product of nature" exception. "The market for monoclonal antibodies is the fastest-growing segment of the pharmaceutical industry." Ledford, *Monoclonal Antibodies Come of Age*, 455 Nature 437, 437 (2008). As judged by sales, five of the top ten pharmaceuticals of 2012 were antibodies, treating a range of illnesses like cancer, rheumatoid arthritis, and Crohn's disease. The substantial investment required to investigate and develop novel monoclonal antibodies is currently driven by the patent system and could be imperiled if the patentability of these molecules were thrown into question by petitioner's sweeping rule. Many genetically engineered antibodies are designed to be similar to the antibodies that occur naturally in the human immune system so that the genetically engineered antibodies will not be attacked by the immune system as foreign. But this very design goal creates a risk that a similar antibody might one day be discovered in nature.

1. Antibodies are Y-shaped proteins generated by the body's immune system as a response to exposure to "bacteria, viruses, and other disease-causing organisms." Murphy, *Janeway's Immunobiology* 127 (8th ed. 2011). Antibodies bind to these "pathogens and their products, to facilitate their removal from the body." *Id.* at 136; *see also* Alberts *et al.*, *Molecular Biology of the Cell* 1018 (2d ed. 1989). The molecule or portion of a molecule to which the antibody binds is called an antigen. Murphy 127.

Antibodies consist of paired heavy- and light-weight polypeptide chains; the two heavy chains bind together in the distinctive Y shape, and one light chain is attached to each arm of the Y. Murphy 128-129. The Y-shape is also divided into two different functional regions. The top portions of the heavy and light chains forming each arm of the Y are called the variable regions because their surface varies widely among antibodies. *Id.* at 128. The variable regions contain the parts of the antibody that contact the target protein, or antigen; thus, it is the differences in these variable regions that primarily determine whether an antibody will bind to a given antigen, akin to the way a lock and key fit together. *See id.* at 136 fig.4.8d (models of antibody-antigen binding); Alberts *et al.* 1016-1017 (measurement of antibody-antigen affinity). The remainder of the molecule is called the constant region because it is identical among large groups of antibodies. Murphy 127, 134.



Antibodies, especially at their variable regions, exhibit an enormous diversity in the body. The number of antibodies present in a person at any given time is limited and changes from person to person based on antigen exposure. Murphy 158. But the multiple means by which the body produces a diverse catalogue of antibodies could theoretically give rise to billions of variations. *Id.* at 166. This natural variability has obvious advantages for combatting different antigens, but historically it limited the study or *in vitro* reproduction of any particular antibody. *Id.* at 730. In 1975, it was shown in Nobel Prize-winning work that identical antibodies of a known antigen specificity could be produced by immunizing a mouse with an antigen to trigger an immune response and then fusing together an immunized mouse spleen cell (responsible for producing the antibody) and a mouse myeloma cell (which produces no antibodies but has the useful property of living indefinitely). Köhler & Milstein, *Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity*, 256 Nature 495, 497 (1975); *see also* Murphy 731. The resulting fusion is called a "hybridoma." *Id.* The hybridoma can be cloned in a laboratory, and all of its clones will produce an antibody with the same antigen specificity. Because these antibodies are all produced from clones and are all ultimately derived from the same initial antibody-producing cell, they are called "monoclonal." *Id.*

Monoclonal antibodies "are valuable research and clinical tools because they are so specific." Drlica, *Understanding DNA and Gene Cloning* 210 (4th ed. 2004). "[O]nce cultured, the cells producing the monoclonal antibodies always produce the same antibody; this consistency is not found when animals are used as antibody sources, since their antibody specificities often change over time." *Id.* at 212. This specificity led some to view antibodies as potential "magic bullet[s]" that might be designed to seek out and destroy specific targets, like cancer cells, while causing no other harm to the body. *Recombinant DNA* 460. But the therapeutic utility of monoclonal antibodies produced from mouse hybridomas is limited.[2] "[T]hey are not identical to human antibodies," and when introduced into a human patient they "will eventually be recognized as foreign proteins and will be cleared from the circulation." *Recombinant DNA* 464; *see also* Chan & Carter, *Therapeutic Antibodies for Autoimmunity and Inflammation*, 10 Nature Revs. Immunology 301, 301 (2010).

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[2] Monoclonal antibodies also have non-therapeutic applications. They can be used, for example, in diagnostic tests to determine whether a sample contains a specific protein. *Biotechnology* 59-60; *e.g.*, Summary of Safety and Effectiveness Data: Ventana

Some of these problems can be overcome by genetic engineering of the antibody produced from the mouse hybridoma. In the 1980s, scientists developed recombinant techniques to create "chimeric" antibodies combining the variable regions of a mouse monoclonal antibody with the constant regions of a human antibody. *See* Chan & Carter, 10 Nature Revs. Immunology at 301; *Recombinant DNA* 464 & fig.23-8. A later strategy, called "humanization," relied on other techniques, such as combining virtually an entire human antibody with only the highly variable sub-regions *within* the variable region of the mouse monoclonal antibody. *See id.* at 464-465; *see also* Murphy 134-135 (explanation and diagrams of "hypervariable" regions within variable region).

Humanized and chimeric antibodies have both enjoyed significant clinical success. For example, Genentech's cancer therapeutic Herceptin® is a humanized monoclonal antibody. *See* Herceptin® (trastuzumab) Prescribing Information 20 (2010). Herceptin® works by binding to a protein found in large amounts on the surface of a particular type of aggressive breast cancer, blocking signals that make the cancer more aggressive, and signaling the body's immune system to destroy the cancerous cells. In clinical trials, it has been shown to extend overall survival for patients with metastatic

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Medical Systems' PATHWAY™ Her 2, at 1 (2000) (mouse monoclonal antibody for use as companion diagnostic to Herceptin®).

breast cancer and, for early-stage cancer, to decrease significantly the chances of the cancer recurring after surgery. *Id.* at 22-29. More than 1.2 million patients have now benefited from this invention.

Herceptin® is just one illustration of the range of therapeutic successes for chimeric and humanized monoclonal antibodies. *See also, e.g.*, Rituxan® (rituximab) Prescribing Information 20 (2012) (chimeric antibody approved to treat rheumatoid arthritis and non-Hodgkins lymphoma); Chan & Carter, 10 Nature Revs. Immunology at 302 tbl.1 (list of monoclonal antibodies in development or already approved for autoimmunity and inflammation diseases). Nevertheless, both humanized and chimeric antibodies retain elements of mouse proteins and can sometimes be recognized by the human immune system as foreign. *Id.* at 301; *Recombinant DNA* 464.

2. The future of monoclonal antibodies is fully "human" antibodies: antibodies constructed in a laboratory with recombinant DNA technologies to be indistinguishable from antibodies produced by the human immune system.[3] The two leading techniques for producing such antibodies—phage display and transgenic mouse antibody production—could both be imperiled by a broad ruling in this case.

Phage display. The first technique relies on an ingenious modification of bacteriophages. "Bacteriophages, commonly called phages, are viruses that infect bacteria." Drlica 108. In phage display, the DNA required to express a fragment of a human antibody is fused to the DNA that encodes the phage's protein coating, which causes the phage to express the antibody fragment on its own surface. Murphy 731-732. So, for example, phages can be made to display the variable region of a human antibody. Because the variable region is what binds to a target antigen, the phage itself now binds to the target antigen.

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[3] "Human" antibodies is a perhaps misleading term used widely in the literature to refer to these genetically engineered proteins. *E.g.*, Chan & Carter, 10 Nature Revs. Immunology at 301. These antibodies are "human" in the sense that they no longer rely on or derive from mouse proteins. As will become clear, they are not "human" in the sense of being found in and taken from human beings. They are a product of laboratory engineering.

To locate an antibody that binds to a specific antigen, researchers can engineer entire libraries of phages that express different antibody fragments, expose the libraries to the antigen, and experimentally sort for the phages that bind well to the antigen. In the search for new therapeutic antibodies, researchers initially built phage libraries by cloning DNA molecules coding for antibody variable regions and then randomly recombining those molecules and fusing them into phages. *E.g.*, Murphy 733 fig.A.16; *see also* Hoogenboom *et al.*, *Antibody Phage Display Technology and Its Applications*, 4 Immunotech. 1, 5-6 (1998). Next-generation phage display libraries rely on more elegant methods. Now, scientists are building synthetic libraries, which have "designed diversities introduced with synthetic DNA." Lee *et al.*, *High-Affinity Human Antibodies from Phage-Displayed Synthetic Fab Libraries with a Single Scaffold Framework*, 340 J. Molecular Biology 1073, 1074 (2004). For example, Genentech scientists have successfully built a library consisting of phages displaying an antibody fragment with a single "scaffold" or "framework"—portions of the antibody molecule, chosen for stability, that all the phages in the library express in common—combined with carefully designed sequence variations only in the hypervariable regions most involved in antigen binding. *See id.* at 1074; *see also* Bostrom & Fuh, *Design and Construction of Synthetic Phage-Displayed Fab Libraries*, *in Antibody Phage Display* 17, 20 (2d ed. 2009) (protocols for choosing framework and generating desired variability). The result of using phage display is a genetically engineered composite antibody sourced from human or human-like DNA, but stitched together in the laboratory. Synthetic phage display libraries are among the most promising current approaches to the search for novel "human" antibodies.

Transgenic mice. An alternative current approach relies on fusing human DNA into the DNA of mice, such that the so-called transgenic mice themselves are capable of producing "human" antibodies. Lonberg, *Fully Human Antibodies From Transgenic Mouse and Phage Display Platforms*, 20 Current Op. Immunology 450, 451 (2008); *see also Recombinant DNA* 255-270 (overview of transgenes). When the mice are immunized with antigens to stimulate an immune response, the variable regions of the antibodies they produce appear to be indistinguishable from the variable regions of antibodies produced by human beings. Lonberg, 20 Current Op. Immunology at 451. The clinical hope is that these antibodies will require less "humanization" than has been required in the past for monoclonal antibodies produced by mouse hybridomas.

3. The current promise of monoclonal antibodies could be imperiled by an overbroad ruling in this case. There is an attenuated sense in which every monoclonal antibody derived from a mouse hybridoma could be characterized as a mere isolated product of nature because it has the same amino acid sequence as the antibody produced by an immunized mouse. This would be a mistake, not the least because the initial immuniza-

tion involved human intervention, not merely natural processes. But this is the type of argument that patent owners could be subject to should the Court adopt a broad version of petitioner's position.

Monoclonal antibodies from phage display or transgenic mice are also not immune from risk. The purpose of these techniques is to isolate DNA molecules that can be used to express fully "human" antibodies—antibodies genetically engineered from the same building blocks used in the human immune system to produce a diverse antibody repertoire. The purpose of genetically engineering antibodies this way is to produce recombinant proteins that will not be attacked as foreign pathogens when introduced into a human patient. But it is at least theoretically possible that an antibody engineered in a laboratory from the same building blocks as used in nature has occurred or may occur at some point in time somewhere in someone's immune system as a result of the body's natural mechanisms for producing an enormous variety of antibodies. Of course, it would be a mistake to regard the genetically engineered antibody as a product of nature merely because a natural analogue might serendipitously occur.[4]

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[4] Petitioner in this very case has relied on ephemeral occurrences of what he claims is "isolation" of genomic DNA—like fragments in maternal plasma (Br. 10 & n.2)—as a reason to find the patents in suit to be drawn to ineligible naturally occurring substances. If petitioner's broad rule prevails, future parties will have a similar incentive to search for or speculate about fleeting natural analogues to a patented synthetic molecule. The fact that any such analogues were unknown or undiscovered at the time of the invention might not be a defense because unlike other doctrines, such as novelty and obviousness, 35 U.S.C. §§ 102, 103, the issue of patentable subject matter under § 101 is not expressly tied to information available before the patent is filed.

But a broad product of nature exception would invite such arguments.

C. Isolated DNA Molecules Are Used In Diagnostic Applications That Would Also Be Jeopardized By A Broad Ruling

DNA-based diagnostic tests are a third example of the innovations potentially at risk if petitioner's broad rule were adopted. Patent eligibility, and the incentive for disclosure that it creates, is especially important for these technologies because the process of obtaining FDA approval for their use as *in vitro* diagnostic devices, 21 U.S.C. § 321(h), is expensive. *See* Ernst & Young, *Beyond Borders: Global Biotechnology Report 2008*, at 70 (2008) (roundtable discussion). Tests developed by laboratories for exclusively "in-house" use are subject to far less stringent regulation than FDA-approved *in vitro* devices.[5] If the key DNA molecule used as a primer or probe for diagnosis cannot be protected by a patent, there will be significant financial pressure to maintain that information as a trade secret and to forgo seeking FDA approval.

1. Amici's tests for the Hepatitis C virus provide a clear example of patent protection paving the way for disclosure, investment in clinical trials, and FDA approval. These tests rely on isolated DNA molecules to serve as the primer for PCR to amplify a portion of the genetic material of Hepatitis C in a sample, if the virus

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[5] Laboratory-developed tests have traditionally not been regulated by the FDA and are instead regulated only indirectly by the Centers for Medicare and Medicaid Services under the provisions of the Clinical Laboratory Improvement Amendments of 1988 (CLIA), Pub. L. No. 100-578, 102 Stat. 2903. CLIA does not require laboratories to establish the clinical validity of the tests.

is present in the sample. *See, e.g.*, COBAS® AmpliScreen HCV Test, version 2.0 Package Insert 1-2 (2007); *see also supra* p. 8 (explaining use of primers for PCR). Isolated DNA molecules also serve as the probes to determine whether the PCR-amplified sample in fact contains the genetic material of the Hepatitis C virus.

After their invention by amici, the isolated DNA molecules used as probes and primers for this diagnostic testing were disclosed in a patent application along with their specific nucleotide sequences. *See* U.S. Patent No. 5,527,669 col. 47, ll. 35-63 (probe claims); *id.* col. 49, ll. 21-45 (primer claims). Those sequences were selected by the inventors so that the probes and primers would hybridize with specific portions of the genetic material of Hepatitis C that are well conserved in various iterations of the virus. *See id.* cols. 9-10. Once the sequence was identified, the primers and probes themselves could be produced by several methods, including direct chemical synthesis. *Id.* col. 6, ll. 44-57. Before these inventions, PCR-based screening for Hepatitis C relied on less accurate probes and primers that had to be applied in multiple steps, introducing sources of possible contamination or error into the diagnostic process. *Id.* cols. 2-3.

Now, after clinical testing, the FDA has approved amici's commercial applications of these patented inventions for both diagnosing Hepatitis C in individual patients and screening donated blood for the virus. *See* COBAS® AmpliScreen Package Insert 15; Summary of Safety and Effectiveness Data: COBAS Amplicor™ HCV Test, v2.0, at 14-19 (2001).

Patent protection for the isolated DNA molecules used as primers or probes has not preempted further diagnostic innovation; several other competitors have been spurred to invent and commercialize other probes and primers to diagnose the virus. *See* Ghany *et al.*, *Diagnosis, Management, and Treatment of Hepatitis C*, 49 Hepatology 1335, 1337-1338 (2009) (listing FDA-approved assays). There are multiple ways to approach the problem, and the patent system has encouraged rather than impeded these advances.

2. Patent-protected DNA molecules also play an important role in the development and clinical validation of companion diagnostic tests. For example, Genentech's Herceptin® therapeutic is indicated only for a particular type of breast cancer characterized by an abundance of receptors for human epidermal growth factor-2 (HER-2). This type of cancer can be identified by DNA-based diagnostic testing for the gene that expresses the HER-2 protein. Ross *et al.*, *The HER-2 Receptor and Breast Cancer*, 14 Oncologist 320, 321-322 (2009). The first such test to receive pre-market approval from the FDA relies on exposing a tissue sample to a fluorescent DNA probe synthetically constructed to hybridize with a stretch of the gene expressing HER-2. *See* Summary of Safety and Effectiveness Data: Oncor® INFORM™ HER-2/neu Gene Detection System 1-2 (1997) (subsequently acquired by Ventana Medical Systems). If the probe indicates that the gene is amplified and thus that HER-2 is overexpressed, the sample likely contains "HER-2 positive" cancer, for which Herceptin® is indicated.

The isolated DNA molecule used for this diagnostic probing was itself disclosed in a patent application. *See* U.S. Patent No. 5,985,553 col. 35, ll. 10-31. As with Hepatitis C diagnostic probes and primers, the patenting of this invention has not impeded further diagnostic innovation by competitors. There are now nine other FDA-approved companion diagnostic tests for Herceptin®, including several other DNA-based *in situ* hybridization tests. *See* FDA, *In Vitro Companion Diagnostic Devices*, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm (updated Nov. 21, 2012). Physicians and patients now have their choice of several clinically validated tests, spurred by the patenting and public disclosure of the first test.

3. A broad ruling that isolated DNA is not a patent-eligible composition of matter would chill this sort of diagnostic innovation and disclosure. If FDA approval is not required for these diagnostic devices, and if there is no commercial incentive to disclose the probe or primer in a patent application, companies are much more likely to opt to keep these probes and primers as undisclosed trade secrets. The result would be less knowledge in the public domain, not more.

* * *

Amici do not mean to say that there are no distinctions between the inventions just described and the patent claims at issue in this case. But as these examples illustrate, the line between natural and man-made compositions of matter is fluid.

The examples also show that when someone invents an isolated compound with some analogue in nature, it is often inaccurate to say that the compound was isolated *from* nature because, in fact, it was synthesized in a lab. Indeed, the very point is that the compound typically cannot be put to practical use as it exists in nature, and the creation of a human-made, isolated form of the compound opens up a range of new uses. A ruling for petitioner would, at best, create significant uncertainty in the biotechnology industry and, at worst, would sweep far beyond anything the Court may have intended.

CONCLUSION

For the foregoing reasons, this Court should affirm the judgment of the Federal Circuit.

Respectfully submitted.

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March 2013

AMICUS CURIAE BRIEF

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FILED
JAN 31 2013
OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,
Petitioners,

v.

MYRIAD GENETICS, INC., ET AL.,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF GENFORMATIC LLC AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

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INTEREST OF THE *AMICUS CURIAE*[1]

Genformatic LLC is a company based in Austin, Texas, engaged in the business of genome sequencing and analysis. All genome sequencing currently practiced involves isolating, purifying, and fragmenting DNA into varying lengths of nucleotide sequences. Thus, whether and to what extent third parties hold intellectual property rights to portions of those nucleotide sequences affects or impairs the ability of scientists, clinicians, and innovators to practice genome analysis and improve the technology of DNA sequencing. Patents on DNA sequences that occur naturally in the genomes of organisms, including humans, also affect or impair the ability of companies such as Genformatic to engage in the business of DNA sequencing and analysis for medical, agricultural, pharmacological, and consumer genomics purposes. Genformatic is concerned that allowing patents to issue on nucleotide sequences that occur naturally in human DNA not only violates this Court's traditional prohibition against patenting natural phenomena but also hinders the advancement of science and technology in this vital area.

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[1] Pursuant to Supreme Court Rule 37.6, counsel for *amicus* Genformatic represents that none of the parties or their counsel authored this brief in whole or in part and that no person or entity other than *amicus* or its counsel made a monetary contribution to its preparation or submission. Petitioners have lodged a blanket consent to the filing of *amicus* briefs, and written consent by respondents to the filing of this brief has been lodged with the Clerk of the Court.

SUMMARY OF ARGUMENT

Sequencing of the human genome represents a revolutionary advancement in the life sciences and presents an opportunity to advance our knowledge of ourselves beyond the conception of even our most visionary thinkers a few decades ago. Since the implementation of the first genome sequencing in the mid-1970s, and especially in the past few years, the speed of sequencing operations has exploded as the cost has plummeted. As with other revolutionary technologies such as personal computers and cell phones, we are approaching an inflection point at which genome sequencing and analysis will become a realistic possibility for the general population. This will allow health care providers to counsel and treat patients based not on generalized norms, but on individual genetic profiles. With this knowledge, the practice of medicine and the development of therapeutic regimens will gradually depend less on trial and error and more on targeted analysis and treatment. Respondent Myriad has recognized the importance of whole genome sequencing ("WGS") and has expressly represented that the claims in its patents "do not preempt or preclude" it. Opp. 17. Whether Myriad or any other holder of such patent rights would make this concession outside this litigation is less certain.

Myriad does not dispute that its claims cover the exact sequences of nucleotide base pairs that occur naturally in human DNA. *See, e.g.*, U.S. Patent No. 5,747,282 (filed May 5, 1998) ("'282 patent"), JA822 (claims 1-7); U.S. Patent No. 5,837,492 (filed Nov. 17, 1998) ("'492 patent"), JA1028 (claims 1-10). But it contends that, because it has claimed "isolated" nucleotide sequences, it has invented something and should be allowed a patent on that section of the human genome sequence. To put Myriad's contention into context, consider that the human genome contains approximately 3 billion nucleotide base pairs. Myriad claims patent rights in sequences as short as 15 base pairs. JA822 (claims 5-6), 1028 (claim 5). With respect to one such claim, researchers observed that Myriad's claimed sequences occurred approximately 340,000 times on chromosome 1 alone, and when extrapolated to the entire human sequence confirms their probable occurrence more than four million times in any human genome.[2]

As an initial step, all genome sequencing techniques currently practiced require randomly fragmenting a DNA molecule into lengths of generally between 30 and about 1,000 base pairs. Sequencing of these individual fragments generates corresponding sequences of nucleotides, called "reads." It is inevitable that DNA molecules having one or more of the nucleotide sequences claimed in Myriad's patents will appear in many different sequence reads produced during sequencing of any human genome.

Nonetheless, Myriad relies heavily on Professor Holman's articles to "debunk the myth" that WGS infringes its patents. *See* Opp. 6, 16. Analysis of his actual methodology and findings reveals that, far from "debunking the myth," Professor Holman underscores the danger of allowing patents on naturally occurring nucleotide sequences. In his study, he identified 4,270 U.S. patents that previously had been labeled as "gene patents."[3] Although he has both a Ph.D. in molecular biology and a law degree, however, he examined only 12.5% of those patents "to make my task manageable." Holman, NATURE BIOTECHNOLOGY at 241. Reading all the claims in this limited sample, he found that almost 70% of the patents he reviewed claimed "DNA molecules that correspond in sequence to at least some portion of a human gene." *Id.* Mathematically extrapolating his findings to all 4,270 patents, his research indicates that there are 2,956 U.S. patents that claim a portion of the human genome – the code of life that occurs naturally in the genetic makeup of every human being. Despite such an overwhelming number of patents, however, Professor Holman advocates reliance on the "notoriously unpredictable undertaking" of claim construction to conclude that a court would ultimately find that gene sequencing did not infringe patents claiming overly broad sequences of DNA. *Id.*

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[2] *See* Thomas B. Kepler et al., *Metastasizing Patent Claims on BRCA1*, 95 GENOMICS 312, 313 (May 2010) ("Kepler"), *available at* http://www.sciencedirect.com/science/journal/08887543/95/5.

Professor Holman's position is consistent with other advocates of the patentability of naturally occurring nucleotide sequences. They insist that it is a better policy to allow such patents under 35 U.S.C. § 101 and to police overreaching through claim construction, anticipation under § 102, obviousness under § 103, and the written-description requirement of § 112. But this Court soundly rejected such an approach in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289, 1303 (2012).

Furthermore, in its 2010 report to the Department of Health and Human Services, the Secretary's

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[3] Christopher M. Holman, *Debunking the Myth that Whole-Genome Sequencing Infringes Thousands of Gene Patents*, 30 NATURE BIOTECHNOLOGY 240, 241 (Mar. 2012) ("Holman").

Advisory Committee on Genetics, Health, and Society observed that the patenting of human genes gives rise to great unpredictability and uncertainty, threatening a "patent thicket" that can inhibit future innovation.[4] This is exactly the danger the court recognized in *Mayo*. *See* 132 S. Ct. at 1303. The Court should not allow those engaged in genome sequencing to be deprived of such a "basic tool[]" of their "scientific and technological work." *Id.* at 1293 (internal quotation marks omitted).

ARGUMENT

I. GENOME SEQUENCING INVOLVES ISOLATING, PURIFYING, AND FRAGMENTING DNA MOLECULES INTO SEQUENCE LENGTHS THAT INEVITABLY FALL WITHIN THE EXPRESS LANGUAGE OF MYRIAD'S CLAIMS

Genformatic believes that a description of gene sequencing will aid the Court in understanding the issues in this appeal. A brief review will put that description in context.

A. An Overview of the Genome

DNA provides the blueprint by which organisms, including humans, are made. The human genetic code is carried in molecules of DNA, arranged in 23 pairs of chromosomes, contained in every cell of the body. Each DNA molecule exists in the form of two separate strands, bound together in a double helix. Each strand contains a sequence of nucleotides: adenine, guanine, cytosine, and thymine, "A, G, C, and T" respectively. These are the only nucleotides in DNA, so the alphabet of heredity consists of only four letters. Contiguous nucleotides on each strand are linked together in linear order by a series of phosphodiester bonds.

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[4] U.S. Dep't of Health & Human Services, *Report of the Secretary's Advisory Committee on Genetics, Health, and Society: Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests* 51 (Apr. 2010) ("HHS Report"), *available at* http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_patents_report_2010.pdf.

Hydrogen bonds bind nucleotides on opposing strands together. The bonds form selectively: A on one strand always pairs with T on the other, while G always pairs with C on the opposite strand. The order in which these nucleotides appear defines an individual's genome.

An essential part of the central dogma of molecular biology is the concept of a "gene." As originally conceived more than 50 years ago, a gene is a DNA sequence transcribed by cellular machinery into messenger RNA, which in turn is translated into a protein or an amino acid polypeptide. Scientists initially assumed that proteins performed all the work required for life, conducting essential enzymatic or biochemical reactions, mediating cellular interactions, precipitating immune responses, and facilitating other functions useful for propagation or survival.

Frequently, there are differences in the expected DNA sequence between two organisms of even the same species. These differences appear in such forms as single nucleotide polymorphisms, or sequence deletions, insertions, or duplications. These changes are often described as "mutations" or "sequence variants." Some but not all of these DNA mutations or sequence variants may manifest in protein changes or alterations in the amino acid sequence of a polypeptide.

Other DNA mutations may alter regulatory features of genes and result in differences in gene expression, in post-transcriptional modifications to RNA, or in post-translational changes to proteins. Yet other genomic variation may impact interactions among genes or result in modifications to the three-dimensional structure of DNA, as well as a growing catalogue of other consequences.

Stated differently, scientists now appreciate that mutations may alter more than the amino acid sequence of a protein. Other effects include modifications to gene transcription (DNA => RNA), RNA splicing, and translation (RNA => protein), and an increasing panoply of genomic interactions. The detection of variants in an individual's DNA sequence allows one to use any previously documented association of those variants with disease susceptibility or drug safety or efficacy to assess an individual's genomic heath risk. That is, one may forecast an individual's probability of exhibiting particular traits or health conditions based upon the detected sequence variation in that person's genome. Disease predisposition and drug-risk assessment are among the primary reasons to do genetic testing in humans and other organisms.

B. A Gene Is Any Sequence of Nucleotides That May Contribute to the Functional and Heritable Characteristics of an Organism

The conception of a gene has evolved considerably in the past 50 years. First articulated as the heritable unit that produces a metabolic enzyme to do the biochemical work of the cell, the concept of a "gene" has now evolved to include any nucleic acid sequence or any combination of nucleotide sequences that produces functional consequences for an organism.[5]

Gregor Mendel, the father of genetics, conceived of a discrete unit conveying inherited characteristics or traits from parent to offspring. Although he was not the first to use the term "gene," Mendel was the first conceptually to distinguish the genotype (the allelic combination of heritable units) from phenotype (the traits or characteristics exhibited by an organism).[6]

Years later, in 1941, Beadle and Tatum developed the hypothesis of one gene–one enzyme, and proposed the mechanism of gene mutation after their experiments exposing mold to X-rays led to errors in metabolic activity.[7] For several years, some erroneously interpreted their work to support the view that proteins themselves were the heritable, information-containing biological molecules.

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[5] *See* Mark B. Gerstein et al., *What is a gene, post-ENCODE? History and updated definition*, 17 GENOME RES. 669 (June 2007). *available at* http://genome.cshlp.org/content/17/6/669.full.pdf+html.

[6] *See* Gregor Mendel, *Versuche über Pflanzenhybriden, in* 4 *Verhandlungen des naturforschenden Vereines in Brünn* 3 (1865). For the English translation, see Gregor Mendel, *Experiments in Plant Hybridization* (C.T. Druery & William Bateson trans., 1901) (1865), *available in updated form at* http://www.esp.org/foundations/genetics/classical/gm-65.pdf.

[7] *See* George W. Beadle & Edward L. Tatum, *Genetic Control of Biochemical Reactions in Neurospora*, 27 PROC. NAT'L ACAD. SCI. 499 (Nov. 1941), *available at* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1078370/pdf/pnas01634-0009.pdf.

Shortly thereafter, in 1944, Avery, MacLeod, and McCarty demonstrated that DNA contained a gene's heritable information (by demonstrating that it could transform harmless bacteria into a lethal strain).[8] Hershey and Chase added to the evidence that DNA, not protein, was the heritable material with experiments in 1952[9] by labeling DNA and protein with different radioactive isotopes and following the fate of those isotopes from parent to progeny.

Watson and Crick completed the puzzle by elucidating the structure of DNA as a double helix.[10] The revelation that nucleotide bases on one strand paired with complementary bases on the other immediately suggested a mechanism for the replication of DNA and the mode of inheritance of traits from nucleic acid sequences. Jacob and Monod subsequently defined the gene as a discrete sequence of DNA, transcribed by cellular machinery into messenger RNA and then subsequently translated into protein.[11] The definition of "gene" as an encoder for instructions for protein synthesis became dogma in molecular biology for approximately 20 years.

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[8] *See* Oswald T. Avery et al., *Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types: Induction of Transformation by a Desoxyribonucleic Acid Fraction Isolated from Pneumococcus Type III*, 79 J. EXPERIMENTAL MED. 137 (Feb. 1944), *available at* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2135445/pdf/137.pdf.

[9] *See* Alfred D. Hershey & Martha Chase, *Independent Functions of Viral Protein and Nucleic Acid in Growth of Bacteriophage*, 36 J. GEN. PHYSIOLOGY 39 (Sept. 1952), *available at* http://jgp.rupress.org/content/36/1/39.full.pdf.

[10] *See* James D. Watson & Francis H. Crick, *Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid*, 171 NATURE 737 (Apr. 1953), *available at* http://www.nature.com/nature/dna50/watsoncrick.pdf.

[11] *See* François Jacob & Jacques Monod, *Genetic Regulatory Mechanisms in the Synthesis of Proteins*, 3 J. MOLECULAR

But genome sequencing and other technological innovations have revealed a far more complex and interconnected genomic landscape. Scientists now appreciate that *noncoding* nucleic acid sequences control the expression of many *coding* sequences and perform other cellular functions. Furthermore, these noncoding domains and the sequences they control may combine in networks of interacting elements *that change during development*. Consequently, the environment or the tissue context in which genes operate may lead to alternate sequence elements or to regulatory changes and functional differences. Scientists no longer understand a "gene" purely as the coding sequence of nucleotides that provides instructions for the synthesis of a particular protein. Instead, the continually evolving notion of a gene now includes both coding and noncoding nucleotide sequence features that operate in interconnected and subtle ways to determine the functional attributes and heritable characteristics of an organism.[12]

BIOLOGY 318 (June 1961), *available at* http://www.pasteur.fr/ip/resource/filecenter/document/01s-000046-03t/genetic-regulatory.pdf.

[12] *See* John A. Stamatoyannopoulos, *What does our genome encode?*, 22 GENOME RES. 1602 (Sept. 2012), *available at* http://genome.cshlp.org/content/22/9/1602.full.pdf+html; Jennifer Harrow et al., *GENCODE: The reference human genome annotation for The ENCODE Project*, 22 GENOME RES. 1760 (Sept. 2012), *available at* http://genome.cshlp.org/content/22/9/1760.full.pdf+html.

C. The Basic Features of Genome Sequencing

Genetic sequencing means determining the precise molecular arrangement of nucleotides in some or all of an individual's DNA, one base pair at a time. It is true that there are other, well-established genetic tests that do not involve sequencing. For instance, fluorescent *in situ* hybridization (FISH) can identify structural mutations, but only those that are large enough to be observed through a microscope. Polymerase chain reaction (PCR) techniques can confirm the existence of known mutations associated with a particular disorder. But tests such as these have neither the utility nor the overall promise of sequencing. For example, pathological conditions may arise from mutations that have not been previously well-characterized, and a single experiment or reaction using these techniques targets only a few mutations. Researchers and clinicians must generally have a good idea of what they are looking for before they order these tests. Because different genotypes can cause the same phenotype, moreover, there might well be a genetic basis for the trait or condition that the ordered test simply fails to reveal.

By contrast, knowledge of the actual sequence of nucleotides gives a complete picture of the portion of DNA at issue or, in the case of WGS, of the entire genome. Acquiring this information has been possible for less than 40 years, and has been practical only in the few years since advances in sequencing technology have dramatically accelerated the speed and reduced the cost of DNA sequencing. *See* HHS Report at 49 ("Such multiplex testing can be useful when a condition involves multiple genetic factors or when one wants to simultaneously test for multiple conditions that have one or more potential genetic causes. In the past, when multiple genetic markers had to be tested, each genetic marker would be tested in a separate test, making testing complex, time-consuming, and expensive.").

1. The Mechanism of Conventional Sequencing

In 1975, Sanger and Coulson described the method of genome analysis that would dominate the industry for the next 30 years.[13] The first step involves breaking open the cell wall to isolate the DNA, then extracting and purifying the DNA from other cellular constituents and biochemicals that bind to the DNA molecule.

Sequencing occurs in several steps. First, the double helix DNA molecule to be sequenced is separated ("denatured") into its two component strands. One of these may be referred to as the "template strand," and the other the "complementary strand." The denatured strands are placed in a "soup" containing all four nucleotides, A, T, C, and G. Most exist in their natural form (dNTPs, where "N" denotes any of the four nucleotides). But there is a comparatively small number that exist as *di*deoxynucleotides (ddNTPs). Both forms will naturally seek a corresponding nucleotide on the template strand, in effect forming a new complementary strand. Because the ddNTPs lack the hydroxyl group to which additional nucleotide bases can attach, however, any new strand formation will end when a ddNTP attaches.

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[13] *See* Frederick Sanger & Alan R. Coulson, *A rapid method for determining sequences in DNA by primed synthesis with DNA polymerase*, 94 J. MOLECULAR BIOLOGY 441 (May 1975), *available at* http://www.sciencedirect.com/science/article/pii/0022283675902132.

To start the sequencing reaction, a short complementary primer molecule is attached to one end of the template strand, and a DNA polymerase enzyme catalyzes the formation of the new strand. The individual nucleotides begin to form hydrogen bonds with the corresponding base on the template strand, extending the new strand, one base at a time, in the 5' to 3' direction. Whenever a ddNTP randomly attaches to the growing strand, however, the absence of a 3' hydroxyl (OH) group precludes further strand extension. The process terminates as to that strand, and the ddNTP marks the last complementary base added in the sequencing reaction. The number of base pairs in the new chain, between the primer and the ddNTP, defines the length of the "read." Because there are many fewer ddNTP molecules than "normal" nucleotides in the mixture, ddNTPs will terminate the newly synthesized strand randomly, resulting in reads of every possible length, up to the longest read length in the process. Significantly, the ddNTPs terminating the new strand are chemically labeled, typically with a dye or fluorophore that facilitates detection of the specific ddNTP terminating each read.

To determine the sequence of the newly synthesized strand, the strands are separated and transferred to a gel or capillary tube in an electric field. The shorter reads move through the field more quickly than do longer reads. As the reads of every length emerge, arranged from shortest to longest, they pass through a laser, which illuminates the dye-labeled ddNTP, identifying the terminating nucleotide. This allows determination of the base sequence of the DNA. Bioinformatic techniques stitch overlapping reads together, revealing the nucleotide sequences of the relevant portion of DNA or, potentially, of the entire genome.

Stitching isolated reads back into a larger sequence requires many sequencing operations to ensure accuracy and completeness. Thus, the most important technological advances in sequencing are those that have enabled an increasing number of parallel sequencing operations. In the years following publication of Sanger's method, researchers developed capillary electrophoresis devices that dramatically increased throughput.[14] As this technology progressed, Sanger sequencing evolved from requiring a lab bench full of gel slabs processing hundreds of base pairs in each run to a single machine with 96, and eventually 384, capillaries processing tens of thousands of base pairs in parallel. In less than four decades, the amount of information that a sequencing operation can reveal has consistently increased as the price of sequencing has consistently fallen.

Sanger biochemistry ultimately led to the mapping of a complete human genome. In 2001, the Human Genome Project Consortium and Celera Genomics simultaneously published their separate reports, describing the first drafts of the human genome sequence.[15] Having a reference genome for comparison, coupled with the advances in technology, has made it possible to identify sequence variants by comparison to the reference sequence. Alignment and mapping of sequence reads to the reference genome has also enabled complete genome sequences of individuals (i.e., other than the reference genome). Significantly, mapping to a reference bypasses the more complex, expensive, and time-consuming task of *de novo* genome assembly. The human genome project also spurred the development of many "next-generation sequencing" methods, further accelerating the breathtaking pace of scientific discovery.[16]

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[14] *See* Harold Swerdlow et al., *Capillary Gel Electrophoresis for DNA Sequencing: Laser-induced Fluorescence Detection with the Sheath Flow Cuvette*, 516 J. CHROMATOGR. 61 (Sept. 1990); Tim Hunkapiller et al., *Large-scale and Automated DNA Sequence Determination*, 254 SCIENCE 59 (Oct. 1991).

[15] *See* J. Craig Venter et al., *The Sequence of the Human Genome*, 291 SCIENCE 1304 (Feb. 2001); International Human Genome Sequencing Consortium, Eric S. Lander et al., *Initial Sequencing and Analysis of the Human Genome*, 409 NATURE 860 (Feb. 2001).

2. The Promise of Next-Generation Sequencing

Genformatic emphasizes two points with respect to the evolution of gene sequencing. First, although sequencing has been possible for less than 40 years, the advances have been remarkable. With continuing advances in next-generation techniques, the possibilities are almost endless. To put the advances into context, Sanger sequencing can process only up to 384 samples in parallel, even with the advances in technology. Next-generation sequencing includes cyclic-array strategies in which "hundreds of millions of sequencing reads can potentially be obtained in parallel." Shendure 2008 at 1136. As capabilities have expanded, sequencing increasingly has become a basic tool of life science. "Sequencing is emerging as a ubiquitous, digital 'readout' for the deep, comprehensive exploration of genetics, molecular biology and cellular biophysics." Shendure 2012 at 1092. Indeed, those in the industry expect it to dominate the entire life science field for the near future and to provide important new tools for clinical medicine.

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[16] A detailed analysis of "next generation" sequencing is far beyond the scope of this brief and is unnecessary for the resolution of the issue presented in this case. For a general overview, see Jay Shendure & Hanlee Ji, *Next-generation DNA sequencing*, 26 NATURE BIOTECHNOLOGY 1135 (Oct. 2008) ("Shendure 2008"), and Jay Shendure & Erez Lieberman Aiden, *The expanding scope of DNA sequencing*, 30 NATURE BIOTECHNOLOGY 1084 (Nov. 2012) ("Shendure 2012").

> Today, sequencing has an increasingly fundamental role in the genetic analysis of human disease and model organism phenotypes as well as in addressing basic questions in organismic and cellular biology. . . . We predict that much of the agenda of biology in the coming decade will be driven in large part by the scientific opportunities afforded by next-generation DNA sequencing technologies.

Id. at 1084.

As technology has advanced, accessibility has increased. Newer sequencing instruments "have fewer infrastructure requirements." Shendure 2008 at 1141. Concomitantly, "[t]he cost of DNA sequencing has plummeted since 2005, from $1,000 per megabase down to a mere ten cents per megabase." Shendure 2012 at 1084 (citation omitted). "The reduction in the costs of DNA sequencing by several orders of magnitude is democratizing the extent to which individual investigators can pursue projects at a scale previously accessible only to major genome centers." Shendure 2008 at 1143.

With the advances in technology, the decrease in cost, and the increase in accessibility, sequencing is poised to move from purely research applications to commercial applications as well. It will soon be possible to sequence an individual's whole genome for less than $1,000.[17] The practice of medicine to date has relied on treatment regimens (including pharmaceutical formulations) generalized to the entire population. This necessarily leads to much trial and error in selecting an effective treatment regimen, as well as to many adverse effects in patients for whom a particular treatment regimen might be harmful. Armed with an individual's entire genetic code, health care providers and pharmaceutical companies will be able to tailor treatment and target conditions to an extent that has been unimaginable to date.[18] Sequencing provides the major stimulus in the evolution to personalized medicine. [19]

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[17] *See* Kevin Davies, *The $1,000 Genome: The Revolution in DNA Sequencing and the New Era of Personalized Medicine* (Free Press, New York 2010).

[18] As with all technological advances, society will have choices to make with respect to such issues as accessibility of genetic information and privacy concerns. *See, e.g.*, Bonnie Rochman, *The DNA Dilemma: A Test That Could Change Your Life*, TIME, Dec. 24, 2012, at 42. Genformatic does not belittle these concerns and proactively considers them in its business plan. But these concerns do not eliminate the benefits that sequencing can provide to individuals and to our society as a whole.

[19] The advances in technology have allowed sequencing to progress from individuals to entire populations. Genome-wide association studies ("GWAS") have generated a rapidly increasing body of knowledge about genetic markers associated with a phenotype of interest (e.g., stroke, multiple sclerosis, or breast cancer). GWAS studies are conducted by identifying thousands of individuals with a phenotype of interest and genotyping those "cases" for hundreds of thousands of genetic markers(typically single nucleotide polymorphisms, or "SNPs"), then comparing the incidence of particular genotypes in cases to the incidence of genotypes in a similar "control" group (which lack the phenotype of interest). Statistical analysis of GWAS data allows

Second, although there are differences among the various next-generation methods, "the great variety of sequencing experiments is a result of distinct combinations of a relatively small set of core techniques." Shendure 2012 at 1091, fig. 3. The advances in next-generation sequencing primarily involve the actual sequencing operations. As with Sanger sequencing, however, the first step remains isolating, purifying, and fragmenting the DNA molecule. Thus, next-generation sequencing remains equally vulnerable to patents on naturally occurring nucleotide sequences.

To put the numbers into context, the Sanger method can sequence a read of up to approximately 1,000 base pairs. The read lengths in next-generation sequencing vary from less than 20 base pairs to several hundred. *See* Shendure 2008 at 1140, table 1; Shendure 2012 at 1187, table 2. Only one sequencing instrument currently available can sequence reads longer than 1,000 base pairs.[20] *See*

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identification of markers associated with the phenotype of interest. For a brief overview and a searchable database, see http://www.genome.gov/gwastudies/.

Note that GWAS studies do not necessarily identify causal mutations, but rather sequence variants linked to a trait. This association allows assignment of an individual to a higher or lower relative-risk category for a particular phenotype depending on the presence or absence of a SNP in their genome. The explosion of GWAS is illustrated by a time series depiction of the rapidly expanding catalogue of GWAS markers and traits. *See* http://www.ebi.ac.uk/fgpt/gwas/#timeseriestab. As GWAS studies move from genotyping hundreds of thousands of SNPs to WGS, the rate of knowledge generation will only accelerate, increasing the probability of identifying causal mutations for disease and other traits.

[20] A higher error rate in calling individual bases tempers this read length advantage. *See* http://www.pacificbiosciences.com/pdf/Poster_High_Throughput_Long_Read_PacBio_RS.pdf.

Shendure 2008 at 1140, table 1; Shendure 2012 at 1187, table 2. Comparing current read lengths to the 3 billion base pairs in the entire human genome, distributed among 23 pairs of chromosomes, it is clear that even the most advanced sequencing technology currently available must isolate, purify, and fragment relatively tiny sequences of nucleotides as a necessary first step. As technology continues to advance, read lengths should continue to increase and costs should continue to decrease. Eventually, there will be a sequencing method that will produce fast, accurate sequence reads comprising tens of thousands of base pairs or more.

II. ALLOWING PATENTS ON NATURALLY OCCURRING NUCLEOTIDE SEQUENCES THREATENS TO INHIBIT FUTURE INNOVATION

Enforcement of patents on naturally occurring nucleotide sequences threatens to inhibit these advances.

A. The Implications of Patent Rights in Naturally Occurring Nucleotide Sequences

The '282 patent contains the following claims:

> 5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.
>
> 6. An isolated DNA having at least 15 nucleotides of the DNA of claim 2.

JA822. As their wording suggests, both of these are dependent claims, referencing claims 1 and 2 of the '282 patent.[21] Although claim 1 and claim 2 ultimately claim the same thing – the nucleotide sequence of the BRCA1 gene – they do so from two different angles. Claim 1 refers to the polypeptide synthesized by the BRCA1 gene, defining the nucleotide sequence by what it makes. Claim 2 refers to the sequence of the DNA itself.

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[21] The '282 patent covers BRCA1. Claim 5 of the '492 patent, covering BRCA2, is analogous to claim 5 of the '282 patent.

The BRCA1 sequence in Myriad's claim 2 (which includes both coding and noncoding portions) is 5,914 base pairs in length, JA822 (claim 2). Because they refer back to claims 1 and 2, claims 5 and 6 cover any sequence "having at least 15 nucleotides" ("15mers"), occurring anywhere along a length of almost 6,000 nucleotides.

Consider that (i) the entire human genome consists of approximately 3 billion nucleotide base pairs, (ii) there are only four nucleotides in DNA, A, T, G, and C, and (iii) modern sequencing methods must first isolate, purify, and segment DNA into reads that typically range from 30 to 1,000 base pairs in length. Given these facts, it is mathematically inevitable that sequences "having at least 15 nucleotides of the DNA of claim 1" will occur somewhere in a genome consisting of a 3 billion base pair sequence of nucleotides. Consequently, it seems inevitable that nucleotide sequences within the express language of these claims will be isolated in the course of sequencing any human genome.

The actual calculations confirm this inevitability. A team of researchers worried that "[o]ne of these claims seemed to us particularly broad, so we investigated it, doing simple calculations to estimate its

---

5. An isolated DNA molecule comprising at least 15 contiguous nucleotides of the DNA molecule of claim 1.

JA1028.

reach." Kepler, 95 GENOMICS at 312. They observed that claim 1 of the '282 patent embodies approximately 1.6 million 15mer sequences, estimating that there are approximately 15 infringing sequences *per human gene* of average length. *Id.* at 313. To experimentally confirm this estimation, the researchers focused on chromosome 1. They empirically verified "over 340,000 matches of claimed 15-mers to the 250 million base pairs of chromosome 1," indicating "about 14 infringing sequences per human gene." *Id.* Not surprisingly, the researchers concluded that "[t]his claim and others like it turn out, on examination, to be surprisingly broad, and if enforced would have substantial implications for medical practice and scientific research." *Id.* at 312.

B. The "Bright Line Prohibition" Against Patenting Natural Phenomena

Even those who support gene patentability under § 101 do not disagree. On October 28, 2010, Professors Christopher M. Holman and Robert Cook-Deegan submitted an *amicus* brief in this case in the court of appeals. This was in the first appeal to the Federal Circuit, prior to this Court's opinion in *Mayo*. With respect to claim 5 of the '282 patent, they wrote that, "[i]n principle, fragment claims such as this provide much broader coverage than claims reciting full-length genes, and would appear to encompass conventional BRCA mutation testing that involves the amplification and analysis of DNA fragments as used in diagnostic testing."[22] The professors demonstrated the breadth of this claim:

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[22] Brief of Amici Curiae Christopher M. Holman and Robert Cook-Deegan in Support of Neither Party at 20, *Association for Molecular Pathology v. United States Patent & Trademark Office*,

> In particular, a recent study found that 80% of the cDNA and mRNA sequences that were contributed to GenBank (and hence presumably published) before the effective filing date of the '282 patent contain at least one DNA fragment falling within the scope of Claim 5, and thus would apparently be encompassed by the claim. [Kepler]. Follow-up studies have shown many "hits" of 15-mer sequences in GenBank sequences that had already been deposited more than a year before patent application, thus implicating 35 USC 102(b).

Holman Amicus Br. at 20-21.

By opining that the sheer breadth of claim 5 would ultimately cause it to fail for lack of novelty, they supported their broader point: that courts should address patents on human genes "more surgically and appropriately . . . with other patent law doctrines [such as claim construction, anticipation, non-obviousness, and written description], or legal and policy solutions addressing problematic enforcement practices" rather than under § 101. *Id.* at 4-5, 20-21. But this ignores a critical issue. Myriad drafted claims 5 and 6, and the USPTO granted the '282 patent, including those claims. Those claims are currently part of an existing United States patent, entitled to the presumption of validity in 35 U.S.C. § 282. And, while "Myriad has only rarely enforced its patents in research, [it] has vigorously enforced its patents against commercial genetic testing, and has selectively enforced its patents in clinical research. . . . *BRCA* research in the United States continues

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653 F.3d 1329 (Fed. Cir. 2011) (No. 2010-1406) (filed Oct. 28, 2010) ("Holman Amicus Br."), 2010 WL 4853323.

only with Myriad's indulgence." Kepler, 95 GENOMICS at 313.[23]

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[23] Myriad's past conduct undermines trusting its continued indulgence.

> The fact that Myriad has allowed research to go forward – most of which infringes its intellectual property – is laudable, but tempered by distrust. If Myriad had a reason to go after researchers, would it do so? *Indeed, it has.*
>
> Myriad restricted *BRCA* testing for clinical research by suing OncorMed and the University of Pennsylvania. All testing at the time was part of research, including trials funded by the National Cancer Institute. Myriad's definition of permissible "research" testing by others was quite narrow; its definition of appropriate testing in its own laboratory, however, was expansive, including clinical testing performed at a time when all health professional recommendations urged testing only in the context of research. OncorMed agreed to test only in research protocols, and Penn was a testing core for multi-institutional trials. It was Myriad that broke from professional standards to do clinical testing outside of research protocols in the early years. *Myriad thus exercised its patent exclusivity in two ways: to establish a U.S. service monopoly and flout clinical guidelines in its own testing and to impose a narrow definition of research on others' BRCA testing.* The Supreme Court may decide "Progress in Science and the useful Arts" is better served by clear legal limits on what can be patented at all, rather than leaving decisions about freedom to do research with patent-holders.

Robert Cook-Deegan, *Law and Science Collide Over Human Gene Patents*, 338 SCIENCE 745, 747 (Nov. 2012) (footnotes omitted, emphases added), *available at* http://people.duke.edu/~ab389/PubList/BCD%20SCience745.full.pdf.

Myriad's gene patents have also empowered it to construct and maintain a proprietary library of gene testing results. *See* Robert Cook-Deegan et al., *The Next Controversy in Genetic Testing: Clinical Data as Trade Secrets* 2 (Nov. 14, 2012) (advance

More importantly, the Court squarely rejected this argument in *Mayo*. "This approach . . . would make the 'law of nature' exception to § 101 patentability a dead letter. The approach is therefore not consistent with prior law." 132 S. Ct. at 1303. The argument that claims 5 and 6 of the '282 patent are so broad that they cannot be valid presents the flipside of the patent holder's argument in *Mayo*. There, the holder "argue[d] that, because the particular laws of nature that its patent claims embody are narrow and specific, the patents should be upheld." *Id.* But the Court refused to resolve the § 101 inquiry based on the breadth or narrowness of the claims, observing that:

> Courts and judges are not institutionally well suited to making the kinds of judgments needed to distinguish among different laws of nature. And so the cases have endorsed a bright-line prohibition against patenting laws of nature, mathematical formulas and the like, which serves as a somewhat more easily administered proxy for the underlying "building-block" concern.

Id. Claims 5 and 6 illustrate the wisdom of this approach. Because a nucleotide sequence is a natural

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online publication; to be published at — EUR. J. HUM. GENETICS —) ("Myriad has access to public databases in interpreting mutations, but outsiders do not have access to Myriad's database."), *available at* http://www.nature.com/ejhg/journal/vaop/ncurrent/pdf/ejhg2012217a.pdf. Hoarding data in this manner has significant implications for WGS. "In an environment in which new technologies, including whole-genome and whole-exome sequencing, are already beginning to change clinical practices in genetic testing, a proprietary database gives Myriad indefinite exclusivity independent of patent protection." *Id.*

phenomenon, it is not patent-eligible under § 101 – no matter its length.

C. Not "Debunking the Myth," But Proving the Point

If the Court allows patents of naturally occurring nucleotide sequences under § 101, genome sequencers face significant practical difficulties. Professor Holman, in attempting to "debunk the myth" that WGS infringes patents such as the patents in suit, underscored these difficulties. To address the "misconception" that "20% of human genes are patented," he contacted the author of the article cited for that proposition, *see* Kyle Jensen & Fiona Murray, *Intellectual Property Landscape of the Human Genome*, 310 SCIENCE 239 (2005), and obtained a list of the 4,270 "gene patents" cited in the article. Holman, 30 NATURE BIOTECHNOLOGY at 240-41. His review of these patents reveals the enormity of the task: "Each patent contains multiple patent claims, sometimes hundreds of claims, so to make my task *manageable* I randomly selected 533 of the 4,270 patents and reviewed all of the claims in each of these patents." *Id.* at 241 (emphasis added). In other words, the "unmanageability" of the task led him actually to review only 12.5% of the cited patents.

Nonetheless, his results were telling. He found that 369/533 patents he examined – 69.2% – claimed "DNA molecules that correspond in sequence to at least some portion of a human gene," presumably because these claims "explicitly mentioned" "at least some portion of the gene's DNA sequence, or the amino acid sequence of the corresponding protein." *Id.* Assuming that his sample was representative, and multiplying the entire sample by the percentage he found, his findings indicate that there are 2,856 U.S. patents that claim patent rights to a portion of a naturally occurring nucleotide sequence in a human DNA molecule.

Despite these overwhelming numbers, Professor Holman concluded that a construction of such claims that is broad enough to endanger gene sequencing would likely lead a court to declare the patent invalid. Specifically, he focuses on the widespread use of the word "isolated" in drafting claims, *id.*, claim language that Myriad has used in the claims at issue. Professor Holman acknowledges that Professor Cook-Deegan "believes that any technology for reading a DNA sequence will necessarily involve isolation and thus constitute infringement if the term 'isolated' is interpreted broadly, a possibility he feels cannot be ruled out," and agrees that "it is impossible to entirely rule out the possibility that a court would interpret a claim to an isolated DNA molecule in the extremely broad sense suggested by Cook-Deegan." *Id.* at 242.[24] Yet Professor Holman is Myriad's primary authority for the proposition that WGS does *not* infringe its patents. *See* Opp. 6, 16.

Professor Holman does acknowledge the uncertainty inherent in relying on claim construction to police overreaching patents. He observes that "the interpretation of patent claims, particularly outside the context of patent infringement litigation, is a notoriously unpredictable undertaking" that is

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[24] This "possibility" would be consistent with the Manual of Patent Examining Procedure (rev. ed. Aug. 2012), which stipulates that claims be given their "broadest reasonable interpretation." MPEP § 2111. The court of appeals has endorsed broad interpretation in the context of claim construction. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (en banc).

"especially pronounced with respect to gene patents." Holman, 30 NATURE BIOTECHNOLOGY at 241. Because "[i]t is not uncommon for the Federal Circuit judges to disagree among themselves as to the proper interpretation of a claim," "some, including at times the Federal Trade Commission, [have] characterize[d] patents as mere 'probabilistic' property rights." *Id.* Nonetheless, he concludes that "the vast majority of these patents would almost certainly not be infringed by WGS, either because they are not gene patents at all, or because they only claim isolated DNA molecules unlikely to be produced in WGS." *Id.* at 244. In any event, he opines that any award of damages for infringement "would most likely be minuscule considering the relative contribution of the patented invention to the sequencing of the entire genome." *Id.*

Far from "[d]ebunking the myth that [WGS] infringes thousands of gene patents," Professor Holman's analysis confirms that there are almost 3,000 U.S. patents whose claims "explicitly mention[]" "at least some portion of the gene's DNA sequence, or the amino acid sequence of the corresponding protein." *Id.* at 240, 241. His reliance on the ultimate invalidity of claims to police overreaching largely leaves the patenting of naturally occurring nucleotide sequences to the "notoriously unpredictable undertaking" of claim construction. *Id.* at 241.

Genformatic asserts that his approach improperly tasks courts and judges with determining the degree to which exclusive rights to naturally occurring sequences of nucleotides inhibit future innovation, a task to which they "are not institutionally well suited." *Mayo*, 132 S. Ct. at 1303. The better approach is to confirm the "bright-line prohibition" against patenting natural phenomena, thereby avoiding the "danger that becomes acute when a patented [composition] . . . forecloses more future invention than the underlying discovery could reasonably justify." *Id.* at 1301, 1303.

D. The Inhibition of Innovation

A decade ago, a group of professors and researchers interviewed 122 directors of U.S. laboratories performing DNA-based genetic tests. They found that "[t]wenty-five percent of respondents reported that they had stopped performing a clinical genetic test because of a patent or license. Fifty-three percent of respondents reported deciding not to develop a new clinical genetic test because of a patent or license. In total, respondents were prevented from performing 12 genetic tests, and all of these tests were among those performed by a large number of laboratories."[25] The cause was not difficult to ascertain: "Almost two-thirds of the laboratory directors in our sample had been contacted by a patent- or license-holder about the laboratory's potential infringement of a patent by performance of a genetic test." Cho, 5 J. Molecular Diagnostics at 5-6 (discussion).

> We conclude that patents and licenses have a significant negative effect on the ability of clinical laboratories to continue to perform already developed genetic tests, and that these effects have not changed substantially throughout the past 3 years. Furthermore, the development of new genetic tests for clinical use, based on

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[25] Mildred K. Cho et al., *Effect of Patents and Licenses on the Provision of Clinical Genetic Testing Services*, 5 J. Molecular Diagnostics 3, 3 (Feb. 2003), *available at* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1907368/pdf/0108.pdf.

> published data on disease-gene associations, and information sharing between laboratories, seemed to be inhibited.

Id. at 8 (conclusion). Notably, BRCA1/BRCA2 were among the genes whose patent holders had contacted the labs. *Id.* at 5 (Effects of Patents and Licenses on Clinical Genetic Testing Services).

In 2010, the Secretary's Advisory Committee on Genetics, Health, and Society confirmed "that patents have been used to narrow or clear the market of existing tests, thereby limiting, rather than promoting availability of testing." HHS Report (transmittal letter). The advisory committee emphasized the danger to innovation: "The substantial number of existing patents on genes and methods of diagnosis also pose a threat to the development of multiplex testing, parallel sequencing, and whole-genome sequencing, the areas of genetic testing with the greatest potential future benefits." *Id.*

To avoid infringement proactively, sequencers of multiple genes or of the whole genome must identify, then try to license, all genes involved in the proposed test. "The alternative of leaving patented genes out of a multiplex test or not reporting the results pertaining to those genes undermines the very clinical utility of multiplex analysis." *Id.* at 50. But identifying, contacting, and reaching an agreement with the patent holders presents enormous difficulties. The advisory committee discovered that ownership of the 4,270 "gene patents" identified in Jensen & Murray's 2005 article was distributed among 1,156 different assignees.

> The existence of so many patents protecting genes, spread among various assignees, creates

> a "patent thicket" – "a dense web of overlapping intellectual property rights that a company must hack its way through in order to actually commercialize new technology." To hack through this thicket to develop a multiplex test, a developer would face several challenges. The developer first would have to identify all the patents requiring licenses. This effort would involve a costly search for relevant patents and an analysis of their claims to determine whether the proposed multiplex test would infringe each particular claim. Once the patents relevant to the test were identified, the developer would have to determine whether licenses were available for each patent. The case studies revealed that such licensing information often is difficult to obtain. Finally, the developer would have to separately negotiate licenses with each individual patent holder.

Id. at 51 (footnote omitted). Although Professors Holman and Cook-Deegan argue that more "surgical[]" doctrines such as claim construction would eventually cure the problem,[26] Holman Amicus Br. at 5, they have acknowledged that, "[i]f 'isolated' is so expansive that full-genome sequencing infringes thousands of individual gene claims, then a serious patent thicket could arise," *id.* at 19-20.

Sequencers could avoid the problem, at least temporarily, by proceeding with development, then defending any infringement suits as they appear. The advisory committee advised against this approach, however, noting that innovators who have already funded projects are "easier prey for patent holders." HHS Report at 52. "Choosing to proceed with a product involves the risk of being sued, and the expense of defending against suits that arise diverts funds that could otherwise be used for innovation." *Id.* Avoidance of potential problems is frequently the best alternative: "the numerous existing patent claims on genes are already affecting the use, if not the development, of multiplex tests in that clinicians are not reporting the results for patent-protected genes in multiplex tests for fear of inviting a lawsuit." *Id.* at 54. Of course, not reporting the entire sequence revealed by WGS defeats the purpose and dulls the promise of combining all available genetic tests into one. Moreover, WGS potentially detects almost all sequence variations, enabling subsequent reanalysis of WGS results to survey for newly identified pathological genetic variation as those discoveries are made.

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[26] To be clear, Genformatic hopes that Professors Holman and Cook-Deegan are correct and indeed believes that there is a likelihood that *all* patents on naturally occurring nucleotide sequences in DNA would eventually be invalidated. But allowing such patents to bypass § 101 effectively sanctions the inhibition of innovation in contravention of this Court's directives.

Turning to a direct discussion of WGS, the advisory committee acknowledged that, because of "the distinct possibility that some patent claims on genes will be infringed by whole-genome sequencing, these patents remain a concern as a potential barrier to the development of whole-genome sequencing." *Id.* at 58. The committee concluded:

> In sum, it appears that test manufacturers are eager to develop – and clinicians are eager to use – multiplex tests, rather than single-gene tests, to carry out genetic testing. These tests would be more efficient than conducting a series of individual tests. Patent claims on isolated

> genes and association patent claims, however, appear to have already created a thicket of intellectual property rights that may prevent innovators from creating these multiplex tests. Similar concerns arise when envisioning the clinical application of whole-genome sequencing. Such scenarios threaten to diminish the usefulness of these promising technologies and their application to patient care.

Id. at 61. Genformatic asserts that this is exactly the sort of inhibition of "future innovation" that concerned the Court in *Mayo*. 132 S. Ct. at 1301, 1303.

CONCLUSION

The judgment of the court of appeals should be reversed, and the patents held invalid.

Respectfully submitted,

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January 31, 2013

AMICUS
CURIAE
BRIEF

No. 12-398

In The
Supreme Court of the United States

ASSOCIATION FOR MOLECULAR PATHOLOGY,
ET AL.,
Petitioners,
v.
MYRIAD GENETICS, INC., ET AL.,
Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR AMICI CURIAE GILEAD SCIENCES, INC., ELAN PHARMACEUTICALS, INC. CONFLUENCE LIFE SCIENCES, INC., EUCLISES PHARMACEUTICALS, INC. & BIOGENERATOR, IN SUPPORT OF RESPONDENTS

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INTERESTS OF AMICI CURIAE

Each Amicus Party, named herein, is an organization that relies on chemical and biotechnology patents; each has a strong interest in ensuring the stability of the patent system as it relates to chemical and biotechnology inventions.[1]

Gilead Sciences, Inc. is a biopharmaceutical company that discovers, develops and commercializes innovative medicines in areas of unmet need.

Elan Pharmaceuticals, Inc. is a biopharmaceutical company that discovers, develops and commercializes innovative medicines in areas of unmet need.

Confluence Life Sciences, Inc. is a biopharmaceutical company engaged in research and development to commercialize innovative medicines in the fields of inflammation and oncology.

Euclises Pharmaceuticals, Inc. is a biopharmaceutical company engaged in research and development to commercialize innovative medicines in the fields of inflammation and oncology.

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[1] No counsel representing Petitioners or Respondents authored this Brief, in whole or in part, and no counsel or party-in-suit made any monetary contribution to preparation or submission of this Brief. Written consent from Counsel of Petitioners is on file with the Court, and consent from Counsel of Respondents will be filed with this Brief.

BioGenerator is a privately funded, non-profit §501(c)(3) organization that facilitates formation of successful, sustainable bioscience companies.

FACTUAL BACKGROUND

After years of intensive investigation and engineering, Myriad researchers synthesized a new and useful DNA chemical compound having a sequence of nucleotides, as recited in Myriad U.S. Patent No. 5,747,282 Claim 2 ("U.S.'282 Claim 2 Synthetic DNA").

U.S.'282 Claim 2 Synthetic DNA does not exist in nature. This is a fact not disputed on the record.

This Myriad Synthetic DNA is useful as an effective and highly-efficient probe in prediction or diagnosis of genetic pre-disposition to ovarian and breast cancers caused by genetic defects in the BRCA1 gene.[2]

I. See Appendix Figure 1 showing Myriad's Discovery Process Resulting in Myriad Synthetic DNA.

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[2] "BRCA1 gene" is a designation assigned by earlier researchers to identify a locus in the human genome that may contain genetic mutations associated with a propensity for development of ovarian and breast cancers.

II. Myriad Natural Product Genomic Screening

As outlined in Figure 1, multipoint linkage analysis was used to localize and refine from Chromosome 17 (~81 million bp) a chromosomal region (6-10 million bp)[3] embracing the BRCAl gene locus (1.5 million bp),[4] which was subsequently mapped using positional cloning.[5] Candidate cDNA clones for the BRCAl genetic locus were identified, and detailed maps of transcripts for the target chromosomal region (600,000 bp) were constructed to provide 65 candidate expressed-sequences (selected by hybridization, direct screening of cDNA library, and random sequencing of subclones).[6] Candidate sequences were then screened within the target chromosomal region, and 21 of the screened sequences were found to constitute key fragments (100,000 bp) of the original BRCAl gene locus including introns and exons (the "BRCA1 segment").[7]

III. Myriad Chemical Transformative Steps

Key fragments of the BRCA1 segment were then transcribed to produce a molecule of pre-mRNA. During this transcription step, the BRCA1 segment was further chemically cleaved, breaking covalent bonds at sites between nucleotide sequences constituting introns and nucleotide sequences

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[3] U.S.'282 at col. 9, lines 29-32 and col. 46, lines 34-38.

[4] U.S.'282 at col. 9, lines 34-37 and col. 46, lines 45-46.

[5] Shattuck Decl., ¶ 4.; U.S.'282 at col. 46-49.

[6] U.S.'282 at col. 49-52.

[7] U.S.'282 at col. 53, lines 22-24 and FIGS 10A-H.

constituting exons, to make a newly-formed mRNA molecule. In the course of more than 20 splicing events, the remaining exon segments of the mRNA were joined forming new covalent bonds. These transformative steps produced mRNA in which the introns were excised from the molecule and the 23 coding exons[8] were covalently linked. The mRNA was then reverse transcribed to produce a full length, intron-free complementary DNA (cDNA) construct, which is a 5,914 bp sequence described in U.S.'282 as SEQ ID No. 1 (and recited in U.S.'282 Claim 2).[9]

SUMMARY OF ARGUMENT[10]

Question certified by the Court in Grant of Writ of Certiorari is:

> "Are human genes patentable?"

Subordinate to this broad Question, as stated, is key question of patent-eligibility under 35 USC §101 of DNA sequences, especially new and useful synthetic DNA constructs.

This is not simply a "gene patenting" case. This case inquires into the scope of eligible substances, specifically synthetic DNA nucleotide sequences, under 35 USC §101 (as "composition of matter," or article of "manufacture," or both).

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[8] U.S.'282 at col. 53, lines 22-24 and FIG. 6

[9] U.S.'282 at col. 53

[10] This Brief was significantly improved by the technical and legal contributions of HDP Attorney Gregory S. DeLassus and HDP Law Intern Nicholas W. Smith, Ph.D.

Thus, a central issue is whether a synthetic, man-made sequence of nucleotides forming a "new and useful" molecule is §101-eligible.

In holding Myriad Synthetic DNA unpatentable,[11] the District Court of Southern District of New York ("SDNY") erred, in two respects:

1) As a matter of Patent Law, the SDNY District Court failed to apply the "made-by-man" fundamental standard for determining §101-eligible subject-matter.

2) As factual error, the SDNY District Court misapplied the "markedly different" test in its analysis of structural and functional characteristics of Myriad Synthetic DNA.

Argument in this Brief specifically targets §101-eligibility of new and useful synthetic, man-made DNA constructs, such as those recited in U.S. '282 Claim 2.[12]

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[11] *Assoc. for Molecular Pathology v. USPTO*, 702 F.Supp.2d 181 (SDNY 2010).

[12] As used throughout this Brief, the following terms are intended to be interchangeable when referring to U.S.'282 Claim 2 SEQ. ID No.1: DNA Sequence, molecule, compound, construct, substance and chemical entity.

ARGUMENT

I. Myriad Synthetic DNA of Claim 2 of U.S. 5,747,282 is Patent-Eligible Subject-Matter under 35 USC §101

A. CAFC Properly Recognized "Made-By-Man" As Fundamental Standard In Subject-Matter Inquiry Under §101

1. Broad Statutory Threshold of 35 USC §101

The threshold of patent-eligibility is defined in 35 USC §101:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.[13]

Enacted in 1952, 35 USC §101 "embodied Jefferson's philosophy that 'ingenuity should receive a liberal encouragement'," and "Congress intended statutory subject matter to 'include anything under the sun that is made by man'."[14] The 1952 Act codifies prior case law. In 1980, *Diamond v.*

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[13] 35 USC §101.

[14] *Diamond v. Chakrabarty*, 447 U.S. 303, 308-309 (1980).

Chakrabarty, as well as subsequent cases, firmly established that patent-eligibility under §101 should have broad scope. Respondent Myriad Genetics, Inc. ("Myriad") invented a synthetic sequence of nucleotides (a chemical compound) which had never existed in nature. This new molecule is a "made-by-man" chemical compound useful as a probe in life-saving diagnosis of human genetic predisposition to ovarian and breast cancers to a high degree of certainty.[15]

This "new and useful" chemical compound is recited in Claim 2 of Myriad U.S. Patent No. 5,747,282 ("U.S.'282") as a DNA sequence defined as SEQ ID NO:1 ("Myriad Synthetic DNA").[16]

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[15] Myriad Synthetic cDNA is useful as a chemical probe to identify cancer-inducing gene-mutations. A woman who tests positive has, on average, an 82% lifetime risk of developing breast cancer and a 44% risk of developing ovarian cancer. These pre-symptomatic individuals, employing appropriate preventive therapies, can reduce their risk of developing breast cancer by approximately 50% (as reported in Journal of the National Cancer Institute), and can lower their risk of developing ovarian cancer by approximately 60% (as reported in New England Journal of Medicine). See: Hall MJ, Reid JE, Burbidge LA *et. al. BRCA1 and BRCA2 mutations in women of different ethnicities undergoing testing for hereditary breast-ovarian cancer.* Cancer. 2009; 115(1):2222-2233.doi: 10.1002/cncr/24200.; *See also* Swisher Decl. ¶¶ 11-13 of SDNY record.

[16] DNA claims at issue in lower courts include: Claims 1, 2, 5, 6 and 7 of U.S. Patent No. 5,747,282 ("U.S.'282"); Claim 1 of U.S. Patent No. 5,693,473 ("U.S. '473"); and Claims 1, 6 and 7 of U.S. Patent No. 5,837,492 ("U.S. '492"). This Brief, however, shall address U.S.'282 Claim 2, only, reciting DNA sequence of SEQ. ID No 1.

Because the SDNY District Court erred in questions of both law and fact, in a manner contrary to statutory intent and meaning of §101,as well as all applicable case law, the Court of Appeals Federal Circuit ("CAFC") properly reversed holdings of the SDNY District Court's adverse ruling on §101-eligibility.[17] Following grant of Petition for Writ of Certiorari, from the earlier CAFC decision, the U.S. Supreme Court remanded this case to the CAFC for disposition in view of rulings in the Supreme Court decision in the *Mayo* case.[18] In a second review of facts and law of the SDNY decision on U.S. '282 Claim 2 §101-eligiblity, the CAFC re-affirmed that Myriad Synthetic DNA:

1) Is §101-eligible; and

2) *Mayo* has no bearing on the issue of DNA patent eligibility.

Diamond v. *Chakrabarty* held that genetically engineered microorganisms are patent-eligible under 35 USC §101.[19] Interpreting 35 USC §101, *Chakrabarty* explained that, "[i]n choosing such expansive terms as 'manufacture' and 'composition of matter,' (modified by the comprehensive 'any'), Congress plainly contemplated that the patent laws would be given wide scope."[20] The *Chakrabarty* Court reviewed the legislative history since the Patent Act of 1793, including the Committee Reports accompanying the 1952 Act, and concluded that "Congress intended statutory subject matter to 'include anything under the sun that is made-by-man'."[21] Thus, the current statutory design sets a broad, welcoming threshold to "embod[y] Jefferson's philosophy that 'ingenuity should receive a liberal encouragement'."[22]

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[17] The patentability of process claims at issue is not discussed herein. Only patent eligibility under §101 of U.S.'282 Claim 2 DNA sequence is discussed herein. This Amicus Brief does not discuss novelty, obviousness, and other patentability issues under 35 USC §102, §103, and §112.

[18] *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289 (2012).

[19] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

Of course, such a broad construction does not mean that §101 is without limit. §101 qualifies specified categories of patentable subject matter by the phrase "new and useful". The *Chakrabarty* Court reiterated that laws of nature, physical phenomena, and abstract concepts are not patentable,[23] and emphasized that "Congress thus recognized that the relevant distinction was not between living and inanimate things, but between products of nature, whether living or not, and human-made inventions."[24] Thus, under *Chakrabarty*, the fundamental question, beside utility and subject matter category inquiries, should be whether the invention is truly "made-by-man", i.e., whether the invention is "the result of human ingenuity and research."[25]

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[20] *Chakrabarty*, at 308.

[21] *Id.* at 309 (citation omitted).

[22] *Id.* at 308-309.

[23] *Id.* at 309.

[24] *Id.* at 313 (emphasis added).

2. CAFC Properly Found Myriad DNA of U.S.'282 Claim 2 as Meeting "Markedly Different" Test and to Be §101-Eligible

To the extent that the Supreme Court in *Chakrabarty* interpreted §101 to require "markedly different characteristics", Myriad U.S.'282 Claim 2 fully satisfies such standard.

Under *Chakrabarty*, "natural product" or "natural phenomena" are exclusions to the broad scope of §101."[26] Under *Chakrabarty's* interpretation of the "new and useful" requirements in §101, an invention is patent-eligible if:
(a) It belongs to a statutory category of subject matter (process, machine, manufacture, or composition of matter);
(b) It is "made-by-man" (i.e., non-naturally occurring substance); and
(c) It has practical utility.

Myriad U.S.'282 Claim 2 Synthetic DNA molecule meets all three requirements.

Firstly, DNA molecules are chemical entities that consist essentially of carbon, hydrogen, oxygen, nitrogen and phosphorous elements. There is no fundamental difference between DNA and other chemicals for purposes of patent law; they are all compositions of matter eligible for §101 inclusion.[27]

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[25] *Id.*

[26] *Chakrabarty*, at 309.

Secondly, Myriad Synthetic DNA is a made-by-man substance. For claims covering a synthetic substance, the human intervention is making or transforming (*i.e.*, to chemically modify, synthesize and characterize) a compound from building blocks (which, in turn, can be basic chemicals such as nucleotides). Myriad Synthetic DNA molecule is a biochemically-synthesized DNA sequence of nucleotides resulting from a series of transformative steps outlined in Figure 1 (Appendix). Such DNA sequence does not exist in nature. Unlike Myriad Synthetic DNA molecule, the naturally-occurring DNA of human Chromosome 17 has fragments of the BRCA-gene coding sequence (in the form of exons and introns) scattered across an 81 million base pair

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[27] Some historical perspective is beneficial here. John J. Doll, former Acting Undersecretary of the USPTO, observes that Plaintiffs' arguments, in many ways, resemble those voiced 30 to 40 years ago when polymer chemistry was an emerging technology. The concerns raised in the current case are similar to those raised when polymers were first patented:

> "At the time, it was argued that patents on the building blocks of basic polymers would devastate the industry. In fact, no such disaster occurred. For example, the issuance in 1965 of a basic patent broadly claiming... ethylene-propylene-diene monomer ("EPDM") rubber... did not preclude the later issuing of patents to different inventors for several copolymers of this type." Doll Decl. ¶ 25.

DNA sequence."[28] Myriad did not purify or extract U.S.'282 Claim 2 Synthetic DNA from natural sources (such as Chromosome 17). Rather, Myriad synthesized U.S.'282 Claim 2 DNA sequence *de novo* from basic nucleotide components, which are themselves artificially synthesized compounds (e.g., oligonucleotide primers). Figure 1 (Appendix) shows the key transformative steps (*i.e.*, chemical manipulations) used to identify and synthesize U.S.'282 Claim 2 DNA.[29] Each of these steps represents the application of careful, intensive and creative efforts by Myriad researchers over a decade.

Thus, but for Myriad's transformative synthetic activity, Myriad Synthetic DNA would not exist as a chemical entity. In short, after laborious effort to identify the BRCA1 gene coding sequence, believed critical for cancer diagnosis, Myriad "human intervention" transformed nucleotide building blocks into a non-natural composition of matter, thus rendering Myriad Synthetic DNA the result of human ingenuity, and not the handiwork of nature.

Thirdly, Myriad Synthetic DNA is a proven-useful diagnostic tool, as evidenced by Myriad's medical and economic success employing Myriad

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[28] Myriad Synthetic DNA is not a natural gene. Genes are "integrated into the chromosome and are not broken or detached from the chromosome." Kay Decl. ¶ 27. Myriad Synthetic DNA has ~0.005% of natural human Chromosomal DNA and does not have the same ordering of nucleotides as the native BRCA1/2 genetic sequence.

[29] See Factual Background, *supra*.

Synthetic DNA compound to predict genetic predisposition to breast and ovarian cancers.[30]

Therefore, under *Chakrabarty* three-fold criteria, Myriad Synthetic DNA is patent-eligible subject-matter under §101.

3. Case Law Is Unanimous That New DNA Molecules Synthesized By Biochemical Transformative Steps Are §101-Eligible

Consistent with the broad interpretation as set forth in *Chakrabarty*, U.S. Courts have upheld §101-eligibility of synthetic compounds including DNA constructs.[31] There is no reported case law in the past 60 years (since the discovery of natural DNA) declaring that a synthetic DNA compound is excludable from §101.

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[30] See description of BRCA*Analysis*™, Crichtfield Decl. ¶¶ 26-30; Skolnick Decl. ¶¶ 19-23.

[31] Case law finding synthetic compounds and materials as §101-eligible include:

(a) *Diamond v. Chakrabarty*, 447 U.S. 303 (1980) (genetically engineered bacteria held to be patentable);

(b) *In re Bergy*, 596 F.2d 952, 960 (C.C.P.A. 1979) (microbe having synthetic DNA plasmid is statutory);

(c) *In re Folkers*, 344 F.2d 970 (C.C.P.A. 1965) (Quinones having electron-transport property are useful);

(d) *Amgen v. Chugai*, 927 F.2d 1200 (Fed. Cir. 1991) (DNA encoding for natural-EPO is patentable);

(e) *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993) (isolated DNA is patentable);

(f) *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Intern., Inc.*, 534 U.S. 124 (2001) (new hybrid corn seed is statutory);

(g) *Plant Genetic Sys. v. DeKalb Genetics Corp.*, 175 F.Supp.2d 246 (D.Conn. 2001) (genetically-modified seeds are statutory);

All prior case law, bearing on new and useful synthetic compounds, has consistently given §101 broad interpretation to conform to the legislative intent of the 1952 Patent Act that any new and useful compound (*i.e.*, Myriad U.S.'282 Claim 2 synthetic DNA construct) "made-by-man", or involving transformative steps, or intervention by man, satisfies the statutory requirement of §101. Up to the present SDNY decision, in every case where a court has explicitly or implicitly evaluated §101-eligibility of a synthetic DNA molecule, the court has ruled for inclusion.[32]

(h) *Chiron v. Genentech*, 268 F.Supp.2d 1148 (E.D.Cal. 2002) (monoclonal antibody binding to breast-cancer antigen is statutory);

(i) *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2005) (recombinant DNA characterized as "non-natural");

(j) *Monsanto v. Good*, 2004 WL 1664013 (D.N.J. 2003) (soybean chimeric gene is statutory);

(k) *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331 (Fed. Cir. 2005) (PHC hemihydrate is synthetic man-made compound as "manufacture" or "composition-of-matter");

(l) *Genentech v. Insmed*, 436 F.Supp.2d 1080 (N.D.Cal. 2006) (insulin-like human growth factor is statutory even without utility).

[32] See case cited at Footnote 31, *infra*.

B. Myriad Synthetic DNA §101-Eligibility Does Not Disturb Any Case Precedent.

In finding for Myriad U.S.'282 Claim 2 synthetic DNA §101-eligibility, the Court need not rely upon any precedent directed to §101-eligibility of a chemical substance based upon case law rulings on purification or isolation of such substance, for two reasons:

(1) Myriad U.S.'282 Claim 2 DNA is a Man-Made synthetic construct.

(2) Case precedent on purification or isolation for determination of §101-eligibility is a fact-driven, but variable and unpredictable, outcome.[33,34]

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[33] Case law finding purified compounds as "new structures" being §101-eligible include:

(a) *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F.95 103 (S.D.N.Y. 1911) (adrenaline composition purified from gland tissue was not "for a degree of purity, and therefore not for a new 'composition of matter.'... it does not include a salt, and no one had ever isolated a substance which was not in salt form, and which was anything like [Patentee's]... [t]hat was a distinction *not in degree, but in kind.* The adrenaline was a new thing "commercially and therapeutically.");

(b) *Merck & Co. v. Olin Mathieson Chem. Corp.*, 253 F.2d 156 (4th Cir. 1958) (naturally occurring vitamin B12 in purified form is patentable);

(c) *Kuehmsted v. Farbenfabriken of Elberfeld Co.* 179 F. 701 (7th Cir. 1910) (purified aspirin is new, useful & patent-eligible);

(d) *In re Bergstrom*, 427 F.2d 1394 (C.C.P.A. 1970) (purified prostaglandin compounds are new);

(e) *In re Kratz*, 592 F.2d 1169 (C.C.P.A. 1979) (purified 2-methyl-2-pentenoic acid, a chemical compound naturally responsible for the flavor of strawberries, was held to be patentable);

(f) *Schering Corp. v. Amgen, Inc.*, 18 F.Supp.2d 372 (D. Del. 1998) (the substantially pure DNA encoding recombinant human interferon-like peptide as substantially-pure DNA sequence is statutory subject matter), affirmed 222 F.3d 1347 (Fed. Cir. 2000).

[34] All cases (since 1874) failing to find new structures, or purified or isolated compounds and materials, as basis for §101-eligible subject matter, as cited by Petitioners or the SDNY District Court, are listed below:

(a) *American Fruit Growers, Inc. v. Brogdex*, 283 U.S. 1 (1931) (combination of a natural fruit and a boric compound carried by the rind or skin of an Orange was not an "article of manufacture," and "does not produce from the raw material an article for use which possesses a new or distinctive form, quality, or property.");

(b) *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293 (1884) (naturally-occurring alizarine is not patent-eligible subject matter because it is not a "new composition of matter."):

(c) *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 129, 130 (1948) (a mixed culture of naturally occurring bacteria was not a patentable advance because no species acquired a *different property or use* - the composition was simply a mixture of bacteria.);

(d) *Gen. Elec. Co. v. De Forest Radio Co.*, 28 F.2d 641 (3d Cir. 1928) (post-filing discovery that patentee's substantially pure tungsten was naturally occurring tungsten, with identical properties as the claimed invention, rendered patentee's invention not a "new metal.");

1. Synthetic DNA of U.S.'282 Claim 2 Is a Man-Made Construct Not "Purified" From Nature.

The DNA of U.S.'282 Claim 2 is the product of a multistep synthesis that involves (1) transcribing the nucleotide segments identified from the BRCAI gene, (2) altering such nucleotide segments by chemically cleaving with 20 or more cleaving and splicing events at 24 splicing sites to form an exon-exclusive mRNA molecule, and (3) reverse transcription of the exon-exclusive molecule into the DNA of U.S.'282 Claim 2, which is a product that does not exist in nature. Furthermore, reverse transcription requires the use of an enzyme, reverse transcriptase, which is not present in a usable form

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(e) *Cf. Am. Wood Paper Co. v. Fibre Disintegrating Co.*, 90 U.S. 566 (1874) (cellulose purified from wood and useful for making paper is patent ineligible);

(f) *Ex Parte Latimer*, 46 O.G. 1638; 1889 Dec. Comm'r Pat. 123 (1889). (The fiber "when it is made free, is in nowise changed or different from its natural construction. There is no chemical combination effected by the treatment which frees it by which the fiber becomes something new or different from the fiber in its natural state.");

(g) *In re Marden*, 47 F.2d 958 (C.C.P.A. 1931) (Rejecting patent on purified vanadium because "pure vanadium is not new in the inventive sense, and, it being a product of nature, no one is entitled to a monopoly of the same.");

(h) *In re Marden*, 47 F.2d 957 (C.C.P.A. 1931) (Purified uranium is patent ineligible);

(i) *In re Merz*, 97 F.2d 599 (C.C.P.A. 1936) (Purified ultramarine is patent ineligible).

in human cells. These transformative steps create the distinct chemical entity of U.S.'282 Claim 2 (not the result of "purification" or "isolation").

2. Patent-Eligibility of DNA of U.S.'282 Claim 2 Is Not Contravened By Any Case Cited By Petitioner.

Every case cited by Petitioner relates to purification or isolation of a known material or lacks a new structure.[35] Conversely, Myriad U.S.'282 Claim 2 synthetic DNA is a man-made, synthetic, and structurally-new and useful molecule. Thus, no case evaluating a known purified or isolated material supports exclusion of §101-eligibility for U.S.'282 Claim 2 DNA.

C. *Mayo* Does Not Compel Reversal of CAFC Decision on §101-Eligibility.

In its July 2011 decision, the CAFC properly reversed the SDNY District Court on matters of law and fact, as to §101-eligibility, of Myriad U.S.'282 Claim 2 DNA.

§101-eligibility of Myriad DNA is fundamentally consistent with the Supreme Court's holding in *Chakrabarty*, and fully supported by firmly established case law developed since enactment of the 1952 Patent Act.

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[35] See cases cited at Footnote 34, *infra*.

Nothing in *Mayo* directs the Supreme Court now to alter the CAFC's holding that U.S.'282 Claim 2 DNA sequence is §101-eligible, as decided by two CAFC reviews (29 July 2011 and 16 August 2012).

Mayo is factually distinguished on two grounds.

Firstly, *Mayo* concerned a diagnostic-method claim, lacking sufficient structural definition to distinguish over natural phenomena. By contrast, U.S.'282 Claim 2 is directed to a DNA composition of matter, namely to a biochemically-synthesized sequence of specific nucleotide content and size.

Secondly, a fundamental component of the *Mayo* Court's examination was whether the Prometheus patent "otherwise forecloses more future invention than the underlying discovery could reasonably justify." This consideration is viewed under the Constitutional requirement of promoting the useful arts, by disclosure of invention in exchange for a government-grant of a limited right to exclude others from using the invention. If the DNA of U.S.'282 Claim 2 were not patent eligible, the discovery would likely not have occurred in the first place. Petitioner's brief urges that researchers would continue BRCA research if Myriad synthetic DNA were held not patent-eligible.[36] However, this position fails to recognize that subsequent researchers would not have the opportunity to do BRCA research had patent protection not incentivized Myriad to discover the DNA of U.S.'282 Claim 2. Perhaps the discovery would have been made by someone else at a later date, but this date may have been far into the future absent the incentive of patent protection.

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[36] Pet. Br. 43.

Upholding §101-eligibility of Myriad U.S.'282 Claim 2 will not preempt an entire field of research because Claim 2 embraces a single nucleotide sequence. Indeed, a broad application of patent ineligibility, however, may, in fact, disrupt the expectations of many chemical and biotechnology patent holders and researchers. These researchers depend on the patent system to secure valuable patent rights, allowing them to attract outside investment.

D. *Bilski* and *Morse* Do Not Support Notion of Myriad Patent Pre-emption

The Court in *Bilski v. Kappos* held that a risk-hedging patent method that would pre-empt use of the approach *in all fields* is not patent-eligible.[37] By contrast, U.S.'282 Claim 2 does not encompass a large number of DNA sequences. Instead, the DNA of U.S.'282 Claim 2 comprises a specific DNA sequence for diagnostic testing of certain pathologies. U.S.'282 Claim 2 does not dominate or encompass all diagnostic testing for genetic mutations. The DNA, therefore, does not pre-empt use of DNA "in all fields."

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[37] *Bilski v. Kappos*, 130 S. Ct. 3218 (2010).

The 1853 case of *O'Reilly v. Morse*[38] is also distinguishable from the facts of the Myriad invention. *Morse* involved a claim on any machinery or process using electromagnetism that would be invented, now or in the future, regardless of the machinery used to perform it.[39] In *Morse*, the use of electrical current was preempted because new ways of using the naturally occurring electrical current, however invented, would infringe the claim. Unlike electromagnetism, Myriad DNA is not naturally occurring. Moreover, U.S.'282 Claim 2 recites no "law of nature" element. The DNA of U.S.'282 Claim 2 is not preempting research because U.S.'282 Claim 2 does not comprise DNA sequences yet to be discovered.

Upholding §101-eligibility of Myriad U.S.'282 Claim 2 will not preempt an entire field of research. However, holding synthetic DNA as patent ineligible would severely hinder research in the biotechnology industry.

This Court has "more than once cautioned that courts 'should not read into the patent laws limitations and conditions which the legislature has not expressed.'"[40] Rendering DNA patent-ineligible as a whole is the province of the legislature.

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[38] *O'Reilly v. Morse*, 56 U.S. 62 (1853).

[39] *Id.* at 112.

at 3226 (quoting . 450 U.S. at 182).

[40] *Bilski* *Diehr*

II. Leahy-Smith America Invents Act ("AIA") reconfirms Myriad Synthetic DNA §101-Eligibility.

The Leahy-Smith America Invents Act (AIA)[41] adopts and recodifies the content of 35 USC §101 verbatim, and further qualifies §101 by this provision:

> "Notwithstanding any other provision of law, no patent may issue on a claim directed to or encompassing a ***human organism***." (Emphasis added.)

The AIA legislative history sheds light on the meaning of this provision: "[T]he U.S. Patent Office has already issued patents on genes, stem cells, animals with human genes, and a host of non-biologic products used by humans, but it has not issued patents on claims directed to human organisms, including human embryos and fetuses. My amendment would not affect the former, but would simply affirm the latter."[42] Thus, AIA §33(a) codifies existing USPTO policy that new and useful synthetic DNA constructs are §101-eligible, while human organisms are not patent-eligible subject matter.[43]

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[41] Public Law 112-29, § 33(a), 125 Stat. 284

[42] 157 Cong. Rec. E1177-04 (testimony of Representative Dave Weldon previously presented in connection with the Consolidated Appropriations Act, 2004, Pub. L. No. 108-199, '634, 118 Stat. 3, 101, and later resubmitted with regard to the AIA; see 149 Cong. Rec. E2417-01).

The Weldon testimony shows that §33(a) applies only to humans as a whole, not to components that make up the human, and avoids applying the patent prohibition on components such as synthetic cells and DNA. Therefore, because a cell is comprised of molecular components such as DNA and other molecules of the cell, these molecules, like cells, should not be included in the "organism" genus of AIA §33(a). Therefore, DNA of Myriad U.S.'282 Claim 2 is not included in the prohibition of "organism."

Lastly, under the AIA, the statutory language for §101 is unchanged from that of the 1952 Act. If Congress intended for a different statutory meaning, Congress would have altered the statutory language accordingly. Thus, DNA should continue to be patent-eligible subject-matter post-AIA.

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[43] Manual of Patent Examining Procedure, section 2105.

CONCLUSION

For the foregoing reasons, Amici herein named, respectfully request:

(1) On the specific question of §101-eligibility of Myriad U.S.'282 Claim 2 DNA, the Court should uphold the CAFC decision; and

(2) On the broader and vague question of patentability of genes, the Court should refer the question to Congress.

Respectfully submitted on 14 March 2013:

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APPENDIX

Q: Is Myriad DNA Construct Same as a Gene? A: NO

Natural Product Genomic Screening

Myriad Chemical Manipulations: > 20 Splicing Events

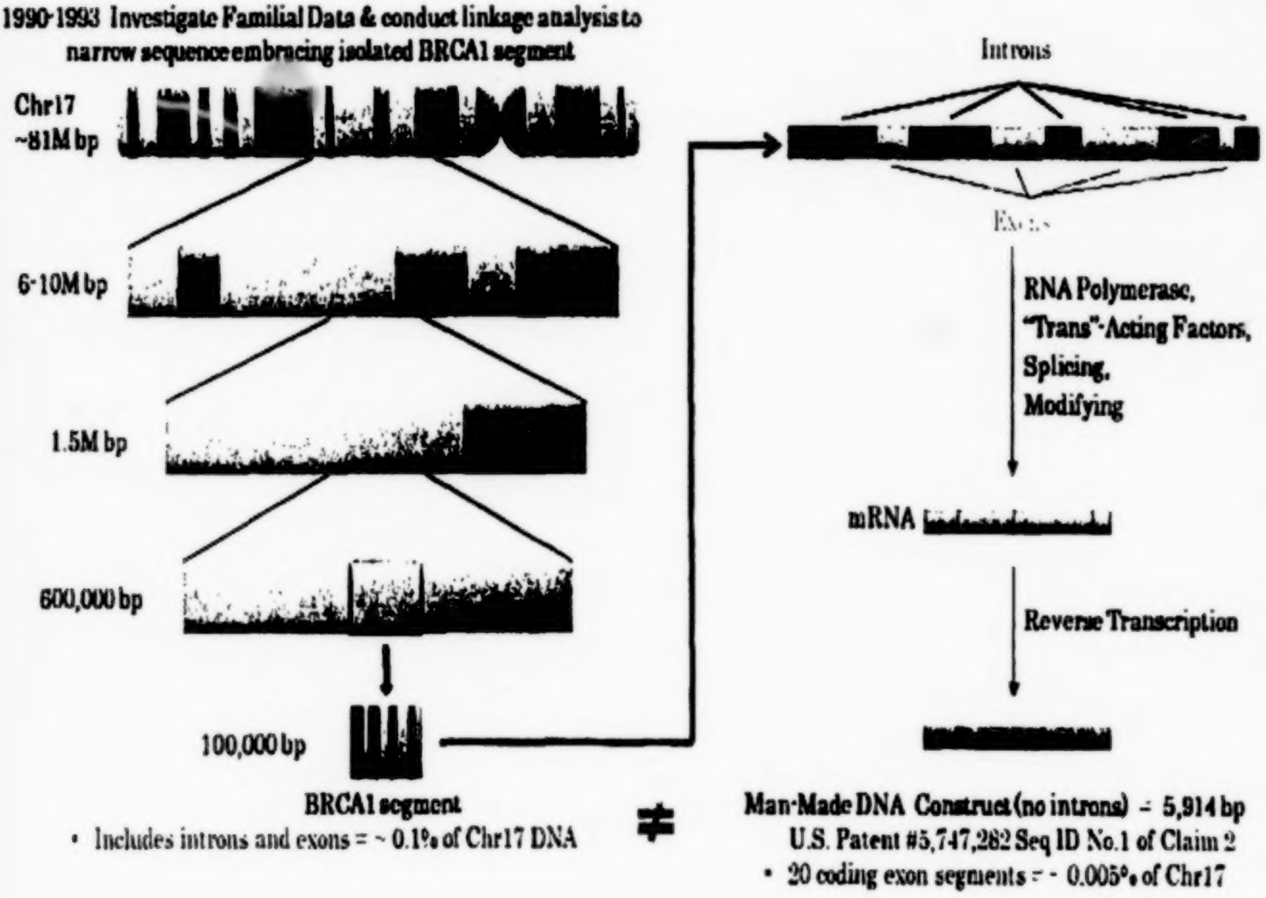
1990-1993 Investigate Familial Data & conduct linkage analysis to narrow sequence embracing isolated BRCA1 segment
Chr17 ~81M bp
6-10M bp
1.5M bp
600,000 bp
100,000 bp
BRCA1 segment
• Includes introns and exons = ~ 0.1% of Chr17 DNA
Introns
Exons
RNA Polymerase, "Trans"-Acting Factors, Splicing, Modifying
mRNA
Reverse Transcription
≠
Man-Made DNA Construct (no introns) = 5,914 bp
U.S. Patent #5,747,282 Seq ID No.1 of Claim 2
• 20 coding exon segments = ~ 0.005% of Chr17

Figure 1:
Transformative-Steps to Make Myriad Synthetic DNA BRCA-Probe Recited in U.S.'282 Claim 2.

AMICUS
CURIAE
BRIEF

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF *AMICUS CURIAE* IMMATICS BIOTECHNOLOGIES, GMBH IN SUPPORT OF RESPONDENTS

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INTEREST OF *AMICUS CURIAE*[1]

Immatics Biotechnologies, GmbH ("Immatics"), is a small, for-profit corporation engaged in the business of identifying and isolating polypeptides that are useful in anti-cancer vaccines. Immatics currently has a number of vaccine compositions in clinical trials, including a renal cell carcinoma vaccine in Phase III trials, a colon cancer vaccine in Phase II trials, and numerous trials against glioblastoma in Phase I. The polypeptides forming the core of these vaccines, much like the polynucleotides at issue in this case, do not exist in nature in an isolated or purified state.

Like many small biotechnology companies, the single most valuable asset held by Immatics is its intellectual property portfolio. It is the only leverage that companies such as Immatics have to secure the continued financing necessary to extend basic research from laboratories to real-world applications. The questions of law and fact decided in this case thus will likely have a bearing on patents and patent applications owned by Immatics.

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[1] No counsel representing any party to the case authored this brief in whole or in part and no counsel or party made any monetary contribution to the preparation or submission of the brief. No person other than the *amicus*, or its attorneys, made a monetary contribution intended to fund the preparation and submission of this brief. The parties have consented to the filing of this brief. Petitioners have lodged blanket consent to the filing of all amicus briefs. Respondent's consent to the filing of this amicus brief has been filed with the Clerk of Court.

SUMMARY OF THE ARGUMENT

Over at least the last 30 years, the United States Patent and Trademark Office ("USPTO") has issued thousands of patents claiming "isolated" nucleic acids, as well as other naturally-occurring chemicals claimed in isolated or purified form. Buoyed by the ability to obtain patents on such subject matter, and urged by the federal government to commercialize the results of federally-sponsored research, investigators began moving out of academic research laboratories and into private industry. As the potential for these technologies became apparent, private equity began pouring money into the industry, hoping to capitalize on the newly discovered therapeutics and diagnostic targets resulting from this research and relying on the issued patents to protect their investments.

Petitioners ask the Court to turn this well-settled order on its head by invalidating patents directed to isolated nucleic acids. According to the Petitioners, this Court's precedent excludes any subject matter containing a nucleotide sequence that exists in nature, arguing that such a patent would, in effect, claim a "product of nature." If this Court finds that "isolated" nucleic acids are unpatenable, it could call into question scores of patents covering this critical subject matter, thereby undermining the viability of these inherently risky but promising ventures.

Nothing in the Constitution, the patent statutes, or this Court's precedent justifies such a drastic action. Rather, the USPTO's practice of requiring natural products to be claimed in "isolated" form is a reasonable measure that ensures that biotechnology and pharmaceutical companies can patent this critical subject matter, without monopolizing anything that already is "readily available to the public."

In the decision below, Judge Lourie and Judge Moore both found "isolated" nucleic acids to be patentable, but for different reasons. Judge Lourie found that isolated nucleic acids are patentable because isolation "breaks covalent bonds" relative to the longer native nucleic acid, thereby resulting in a new chemical entity. Judge Moore reasoned that, if analyzed on a blank slate, she would require the product to have a "substantial new utility" relative to its natural function in order to satisfy 35 U.S.C. § 101. While Immatics agrees that the generation of a novel chemical entity or demonstration of a new utility would be sufficient to satisfy 35 U.S.C. § 101, these are not necessary requirements.

Immatics therefore urges the Court to find that claims directed to isolated products of nature – such as the isolated nucleic acids at issue in this case – satisfy 35 U.S.C. § 101 so long as the claimed subject matter covers only compositions that (1) do not exist without human intervention and (2) have a substantial utility tied to this isolated form. The statute does not – and should not – require a change in either the chemical structure or the "essential character". This principle is consistent with the plain language of 35 U.S.C. § 101, and the cases principally relied upon by Petitioners: *Diamond v. Chakrabarty*, 447 U.S. 303, (1980), *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1 (1931), and *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948). As explained below, none of these cases requires the claimed subject matter to be directed to a novel chemical structure or a completely new activity in its isolated form.

The Petitioners characterize the test for patentability of naturally derived products as whether the inventor has transformed the "essential character" of the natural product such that it has a "distinctive name, character, or use". According to Petitioners, the isolation of a nucleic acid cannot transform it to something having a "distinctive name, character, or use" because the nucleotide sequence is its "essential character". Even assuming that this is a test for patent eligibility (which is not the case), the Petitioners have mischaracterized what subject matter satisfies this test.

The "distinctive name, character, or use" test is derived from *Hartranft v. Wiegmann*, 121 U.S. 609 (1887). In that case, the Court cites India rubber shoes as an example of subject matter that would satisfy this test, explaining that, by placing the rubber into a mold, it is transformed "into a new form capable of use and designed to be used in such new form." Therefore, contrary to the Petitioner's characterization, this test does not require a change to the "essential character" of the natural product, but that the natural product be placed into a "new form capable of use and designed to be used in such new form." An isolated nucleic acid would clearly satisfy this test, because most practical uses of the nucleic acid require it to be removed from its natural context and maintained in a substantially pure form.

This is an important point, because many new biologics and pharmaceuticals are essentially purified or synthetic versions of naturally occurring compounds. The mere fact that such compounds exist in nature does not make them readily available for human utility. Indeed, in most cases, such compounds have no practical utility in context in which they are found in nature. The process of identifying and commercializing such products is an expensive and time-consuming proposition, often costing years of effort and hundreds of millions of dollars, with no guarantee that the candidate will ever become a viable product. For small biotechnology companies like Immatics, the only leverage that they have to ensure continued funding is the ability to patent the compounds at the core of their products.

Given that the federal government has granted such patents for at least 30 years without any action from Congress, the Court should not act to invalidate these valuable property rights.

The decision of the Court of Appeals for the Federal Circuit should therefore be affirmed.

ARGUMENT

I. The Term "Isolated" Limits the Claims to Non-Naturally Occurring Compositions Comprising the Natural Product

The USPTO has granted patents on natural products in their isolated and/or purified form for over 130 years. *See, e.g.*, U.S. Pat. No. 141,072, cl. 2 (filing May 9, 1873) (claiming "[y]east, free from organic germs of disease, as an article of manufacture"). This does not mean that patents issue for products as they exist in nature. By reciting that the product is isolated, the patentee is explicitly claiming the product removed from its natural context. As explained by the USPTO:

> A patent claim directed to an isolated and purified DNA molecule could cover, e.g., a gene excised from a natural chromosome or

> a synthesized DNA molecule. An isolated and purified DNA molecule that has the same sequence as a naturally occurring gene is eligible for a patent because (1) an excised gene is eligible for a patent as a composition of matter or as an article of manufacture because that DNA molecule does not occur in that isolated form in nature, or (2) synthetic DNA preparations are eligible for patents because their purified state is different from the naturally occurring compound.

66 Fed. Reg. 1092, at 1093 (Jan. 5, 2001). In addition, the form of the product that is being claimed must have a specific and substantial credible utility in the form in which it is claimed. *Id.* Thus, the USPTO's claim format limits isolated nucleic acid claims to subject matter that (1) does not exist in nature, and (2) is useful. This claim format does not require the claimed composition to possess either a novel chemical structure or a new activity relative to the product in its natural state.

Isolated compounds derived from natural sources, such as the isolated nucleic acids at issue in this case, are, by definition, man-made. Although it is often convenient to describe them in terms of chemical structure or nucleotide sequence, such "pure" or "isolated" compositions never exist in nature. Rather, they are inevitably found in complex associations with other compositions. The isolation process sometimes results in distinct chemical entities, such as the isolated nucleic acids in this case. *Ass'n for Molecular Pathology v. U.S.P.T.O.*, 689 F.3d 1303, 1328 (Fed. Cir. 2012). Other times, the result is a highly purified compound. *See, e.g., Parke-Davis v. Mulford*, 189 F. 95, 103 (S.D.N.Y. 1911) (purified adrenaline); *Merck & Co. v.*

Olin Mathieson Chemical Corp., 253 F.2d 156 (4th Cir. 1958) (vitamin B12). In each case, however, the product simply does not exist in nature in an isolated form. An isolated form of such a product thus is a purely artificial, non-naturally occurring composition of matter.

II. The USPTO's Claim Format Is Consistent With the Constitution, the Patent Laws, and the Court's Precedent

The rationale for allowing such a claim is well-grounded in the Constitution, the statutes, and the case law.

A. Patenting of Isolated Products of Nature Is Consistent With the Constitutional Purpose of the Patent Laws

The Constitution does not require a claimed compound to have a formally "new" chemical structure or new function to justify a patent. Article I, Section 8 of the Constitution authorizes patents "[t]o promote the Progress of Science and useful Arts." As explained by the Court:

> Congress may not authorize the issuance of patents whose effects are to remove existent knowledge from the public domain, or to restrict free access to materials already available. Innovation, advancement, and things which add to the sum of useful knowledge are inherent requisites in a patent system which by constitutional command must 'promote the Progress of useful Arts.' This is the standard expressed in the Constitution and it may not be ignored.

Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 6 (1966). Thus, the Constitution only prohibits patents that "remove existent knowledge from the public domain" or "restrict free access to materials already available." Assuming that a claimed product satisfies 35 U.S.C. §§ 102 and 103, a patent thereto cannot "remove existent knowledge from the public domain." Likewise, the term "isolated" inherently limits the claim to subject matter that does not naturally occur. These claims therefore do not "restrict free access to materials already available." Such patents are therefore consistent with the Constitutional purpose of the patent laws.

The patent laws likewise do not prohibit patenting of isolated products of nature. Section 101 only requires that the patent claims be limited to "new" and "useful" subject matter. 35 U.S.C. § 101. This is expansive language, which "includes anything under the sun . . . made by man," and certainly any "nonnaturally occurring article of manufacture or composition of matter." *Chakrabarty*, 447 U.S. at 309 (quoting S. Rep. No. 82-1979, at 5 (1952); H.R. Rep. No. 82-1923, at 6 (1952)). As long as the claimed product does not naturally exist in isolated form, it must be considered a non-naturally occurring article of manufacture or composition of matter.

B. This Court's Precedent Only Prohibits Claims That Encompass a Natural Phenomenon as it Exists in Nature

The Court's recent ruling in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), stands for the unremarkable proposition that a patent must do more than simply claim a law of nature.

The claims at issue in *Mayo* recite a "law of nature – namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective and cause harm." *Mayo*, 132 S. Ct. at 1296. In addition to this "law of nature," the claims recite only two steps: administering a drug to a patient and observing the concentration of the metabolites in the blood. The claims of *Mayo* are thus limited only to: (1) generating the natural phenomenon by administering the drug and measuring the concentration of the metabolite (both of which were well-established in the art); and (2) observing the natural phenomenon (the correlation between concentration of the metabolite and the appropriate dosage of the drug). For this reason, the Court held that the claims do not satisfy 35 U.S.C. § 101 because the recited steps, "when viewed as a whole, add nothing significant [to the law of nature] beyond the sum of their parts taken separately" and thus effectively claim the law of nature itself. *Id.* at 1298.

This holding is along the same lines as *Bilski v. Kappos*, 130 S.Ct. 3218 (2010), *Gottschalk v. Benson*, 409 U.S. 63 (1972), and *Parker v. Flook*, 437 U.S. 584 (1978). In each of these cases, the critical issue was whether the claims cover a law of nature, natural phenomenon, or abstract idea itself, as opposed to a concrete application thereof. Such concepts are presumed to be old because they do nothing more than "reveal[] a relationship that has always existed," *Flook*, 437 U.S. at 593 n.15, and therefore "are consistent with the notion that a patentable process must be 'new and useful,'" *Bilski*, 130 S. Ct. at 3221. For process claims, 35 U.S.C. § 101 requires that "[t]he process itself, not merely the mathematical algorithm, must be new and useful." *Flook*, 437 U.S. at 591. That is, the patent may not effectively claim subject matter that exists independent of any human intervention.

Therefore, the critical question under *Mayo* is whether the patent is limited to man-made subject matter. If so, then the subject matter is patent-eligible. If, however, the patent reads on subject matter that exists without human intervention, the claim is patent-ineligible. This concept is consistent with the USPTO's interpretation of *Chakrabarty*. As noted by the *Chakrabarty* Court, Congress intended Section 101 to broadly encompass "everything under the sun . . . made by man." *Chakrabarty*, 447 U.S. at 309 (internal citations and quotations omitted). Thus, where a claim is limited to a "non-naturally occurring article of manufacture or composition of matter," 35 U.S.C. § 101 is satisfied. *Id.* at 303.

Petitioners argue that *Funk Brothers* expands this rule to prohibit patenting of naturally-occurring products, "when [the] compositions function as they naturally would, even when human ingenuity led to their packaging in a more useful form." Pet. Br. at 29. This is not the holding of *Funk Brothers*. Each of the claims at issue in that case relates to inoculants comprising non-specific "non-inhibitive strains of . . . Bacteria." *Funk Bros.*, 333 U.S. at 128 n.1 (quoting U.S. Patent No. 2,200,532, cl. 4 (filed Aug. 24, 1938)). Thus, the patent does not claim a specific composition, but a general concept of "mutually non-inhibitive strains." As explained by Justice Frankfurter:

> [Patentee] appears to claim that since he was the originator of the idea that there might be mutually compatible strains and had practically demonstrated that some such strains exist,

> everyone else is forbidden to use a combination of strains whether they are or are not identical with the combinations that [Patentee] selected and packaged together.

Id. at 133 (Frankfurter, J., concurring). The rejected claims in *Funk Brothers* were not invalid because they claim a specific product that "functions as it naturally would." Rather, the claims were rejected because they effectively claim a natural phenomenon without an appropriate structural limitation. *See Funk Bros.*, 333 U.S. at 129-31; *cf. Mayo*, 132 S. Ct. at 1290-91. In contrast, claims to isolated nucleic acids are directed to specific products that never exist in nature in such a form. As such, neither *Funk Brothers* nor *Mayo* holds that products derived from a natural source, such as those at issue in this case, are unpatentable under 35 U.S.C. § 101.

C. Neither *Chakrabarty* nor *American Fruit Growers* requires anything beyond non-naturally occurring subject matter

Petitioners further argue that a composition is not patent eligible unless it "has a distinctive name, character and use," irrespective of whether it has a different chemical structure or character from anything existing in nature. Pet. Br. 28. According to Petitioners, isolated DNA does not have a distinctive name, character, or use or markedly different characteristics from naturally occurring DNA because the genetic sequence remains essentially the same. *Id.* at 30-31. However, neither *Chakrabarty, Funk Brothers*, nor *American Fruit Growers* holds that subject matter must "have a distinctive name, character, or use" or "markedly different characteristics" in order to be "new" within the meaning of 35 U.S.C. § 101. Even if these cases did so hold, Petitioners misinterpret what is meant by these standards.

(i) The phrase "having a distinctive name, character, and use" relates solely to whether something is considered an article of manufacture

The "distinctive name, character, or use" and "markedly different characteristics" language from *Charkrabarty* and *American Fruit Growers* is not a limitation on patentable subject matter. In both cases, this language is attributed to *Hartranft v. Wiegmann*, 121 U.S. 609 (1887). *Hartranft* was not a patent case, but a customs case addressing whether a cleaned, ground, and etched shell is considered a "shell" or a "manufacture of a shell" for the purpose of calculating the appropriate customs duty. *Id.* at 612-13. The Court held that the shells at issue were not a "manufacture" because "[t]hey had not been manufactured into a new and different article, having a distinctive name, character, or use from that of a shell." *Id.* at 615.

The Court's reliance on *Hartranft* logically relates only to whether the subject matter at issue was an "article of manufacture." This question was critical in both *Chakrabarty* and *American Fruit Growers*. In *Chakrabarty*, the USPTO argued that a genetically modified living organism could not be considered an "article of manufacture." *Chakrabarty*, 447 U.S. at 310-11. Similarly, the sole issue before the *American Fruit Growers* Court was whether "an orange, the rind of which has become impregnated with borax . . . [is] a 'manufacture,' or manufactured article." *Amer. Fruit Growers*, 283 U.S. at 11. Neither *Chakrabarty* nor *American Fruit Growers* requires all products to have a "distinctive name, character, and use" or "markedly different characteristics" in order to satisfy 35 U.S.C. § 101. Rather, demonstrating that the product has a "distinctive name, character, and use" or "markedly different characteristics" is sufficient precisely because it shows that the subject matter is an "article of manufacture."

(ii) Even if a claimed product must have a "distinctive name, character, and use" or "markedly different characteristics," this standard does not require a transformation of the "essential character" of the claimed product

Even if *Chakrabarty* and *American Fruit Growers* could be read to limit Section 101 to products "having a distinctive name, character, and use," Petitioners misconstrue what is meant by this language. According to Petitioners, isolated nucleic acids are not "new" because they contain a nucleotide sequence that naturally occurs in nature, thus retaining the same "essential character" as the naturally occurring composition. *See Ass'n for Molecular Pathology v. U.S.P.T.O.*, 689 F.3d 1303, 1355 (Fed. Cir. 2012) (Bryson, J., concurring in part and dissenting in part); Pet. Br. at 35. Thus, Petitioners argue, whether the product is different in form from its naturally occurring counterpart is irrelevant unless there is a transformation of its "essential character." *See* Pet. Br. at 35. This argument is not supported by the Court's precedent.

Hartranft again is instructive. The Court distinguished the shells in that case from another case involving India rubber shoes, noting that:

> it was held that India rubber shoes, made . . . by simply allowing the sap of the [I]ndia rubber tree to harden upon a mould, were a manufactured article, because it was capable of use in that shape as a shoe, and had been put into a new form capable of use and designed to be used in such new form.

Hartranft, 121 U.S. at 615 (citing *Lawrence v. Allen*, 48 U.S. 785 (1849)). The shoes at issue in *Lawrence* are nothing more than hardened India rubber sap. The human intervention does not change the "essential character" of India rubber sap as a raw material; it merely hardens as it would in nature. Nonetheless, human intervention, by placing the sap in a mold to harden, creates a product "having a distinctive name, character, and use" by transforming the raw material "into a new form capable of use and designed to be used in such new form." *Id.* The "transformation" did not change the "essential character" of the India rubber, but harnessed that "essential character," using human ingenuity, to craft it into a form suitable for use.

Taq polymerase provides another example. Taq is naturally produced by *Thermus aquaticus*, a bacterium found in hot springs. James H. Davis & Michele M. Wales, *The Effect of Intellectual Property on the Biotechnology Industry*, 50 Advances in Genetics 427, 437 (2003). Because it is derived from an organism that lives in high temperatures, Taq is heat stable and does not lose activity when subjected to high temperatures. *See* Smithsonian Institution Archives, The History of PCR, RU 9577, http://siarchives.si.edu/research/videohistory_catalog9577.html (last accessed March 12, 2013).

The inclusion of Taq into a process called polymerase chain reaction ("PCR") is often cited as the single most important technological advance to the modern biotechnology industry, an achievement for which the inventors received the Nobel Prize in Chemistry. In the original iterations of PCR, new polymerase enzyme had to be added to the reaction mixture after each heat cycle, because the high temperature permanently deactivated the enzyme. *Id.* Because of its stability, Taq only needs to be added to a PCR reaction mixture once, thus greatly reducing the costs and the time of performing the process, and permitting easy automation. *Id.*

There is no principled reason why Taq should be excluded from patent eligibility. The identification and characterization of this enzyme is a significant technological advance, from which the public obtains a substantial benefit. Yet the properties of Taq that make it so attractive for PCR are a consequence of its structure and function in the natural world. In nature, just like in PCR, Taq functions as a thermostable enzyme that catalyzes the amplification of a nucleic acid. Nonetheless, assuming that 35 U.S.C. §§ 102 and 103 are satisfied, a claim to isolated Taq cannot "remove existent knowledge from the public domain." *Graham*, 383 U.S. at 6. Moreover, because Taq only exists in nature within a bacterium at a low concentration, isolated Taq is not a "material [] already available" to the public. *Id.* The only way that Taq has a practical utility is by isolating it from its natural source. Like the India rubber example, "transformation" of Taq to an isolated form does not change the "essential character" of enzyme itself, but instead harnesses that "essential character," using human ingenuity, to craft it into a form suitable for use in PCR.

The same is true of isolated nucleic acids. Like Taq and the India rubber in *Lawrence*, naturally occurring nucleotide sequences require human intervention to transform them into something useful. By removing nucleic acids from their natural context and placing them into an isolated form, they become available for uses that are otherwise unavailable, such as:

- molecular probes for identifying related nucleic acids, *see* U.S. Patent No. 5,310,651 (filed Sept. 9, 1991);
- a gene replacement therapeutic, *see* U.S. Patent No. 6,262,035 (filed Oct. 1, 1998); and
- transforming cells into cellular "factories" for producing a variety of end products, *see* U.S. Patent No. 5,866,382 (filed Nov. 3, 1994).

Human ingenuity thus is required to place a naturally occurring nucleotide sequence into a "new form capable of use and designed to be used in such new form" by placing it in an isolated composition. *Hartranft*, 121 U.S. at 615. Consistent with *Chakrabarty*'s and *American Fruit Growers*' reliance on *Hartranft*, isolation of a nucleic acid results in a product "having a distinctive name, character, and use" from anything that occurs in nature.

(iii) The dissent's analogy to "snapping a leaf from a tree" and "newly discovered minerals" does not work

In his dissenting opinion, Judge Bryson argued that isolating a nucleic acid does not result in a "new" product, analogizing it to the act of removing a branch or a leaf from a tree or extracting a mineral from the earth. *Ass'n for Molecular Pathology*, 689 F.3d at 1350 and 1353 (Bryson, J., concurring-in-part and dissenting-in-part). However, "isolated" leaves already exist in nature without human intervention, as they often become separated from trees through natural forces, such as strong gusts of wind. Nor is human intervention required to generate a newly discovered mineral. Thus, the human intervention of removing a leaf from a tree or a mineral from the earth does not result in a new form of that leaf or that mineral. However, were one to process that leaf or mineral into a form that did not previously exist (such as a purified extract from the leaf or highly purified form of the mineral), and a patent claim were limited to that non-natural form, that transformation would result in a "new form capable of use and designed to be used in such new form." *Hartranft*, 121 U.S. at 615.

Contrary to the dissent's analogy, pharmaceuticals and biologics cannot simply be picked off of a tree or dug up from the earth. For example, the chemical entity paclitaxel (Taxol®) is naturally produced in the bark of the Pacific yew tree, *Taxus breviolia*. Jordan Goodman & Vivien Walsh, *The Story of Taxol, Nature and Politics in the Pursuit an Anti-Cancer Drug* (2001). Paclitaxel has proven to be very useful for treatment of various cancers. However, at the time that paclitaxel was identified, there was no indication that the yew tree had any practical use, much less that it harbored anti-cancer compounds. *See id.* at 51-52. Paclitaxel is very difficult to obtain from the yew tree: 1,200 kg of bark yields only 1 kg of pure product. *Id.* at 81. The simple fact is that, without being isolated, the chemical entity paclitaxel has no practical utility at all.

The question therefore should be: does the claimed subject matter as a whole exist independent of human intervention? In *Mayo*, *Bilski*, *Flook*, *Benson*, and *Funk Brothers*, the answer was "no" because in each case the patent effectively claimed an underlying abstract idea or natural correlation. *See Mayo*, 132 S. Ct. at 1298, *Bilski*, 130 S. Ct. at 3221; *Flook*, 437 U.S. at 585; *Benson*, 409 U.S. at 64, *Funk Bros.*, 333 U.S. at 133 (Frankfurter, J., concurring). In *Chakrabarty*, the answer was "yes" because the claimed organism does not exist independent of human intervention. *Chakrabarty*, 447 U.S. at 303. Isolated nucleic acids, like the invention in *Chakrabarty*, are claimed in a form that absolutely requires the intervention of humans in order to exist. Branches, leaves, and minerals do not.

In view of the foregoing, there simply is no categorical rule that prohibits patenting of natural products in isolated form. Indeed, the clear language of 35 U.S.C. § 101 only requires that claimed "invention or discovery" be: (1) new; (2) useful; and (3) a process, article of manufacture, or composition of matter, or an improvement thereof. 35 U.S.C. § 101. Nor does the Court's precedent prohibit claims to subject matter limited solely to non-naturally occurring articles of manufacture or compositions of matter. Consistent with *Mayo* and *Funk Brothers*, such products are patentable as long as they do not claim a natural phenomenon per se. Thus, as held by *Chakrabarty*, a non-naturally occurring composition derived from a natural source, such as the isolated nucleic acids at issue in this case, should be considered "new" within the meaning of 35 U.S.C. § 101.

III. Patents Covering Isolated Biological Products Are Critical to the Financial Viability of Biotechnology Companies and Are Deserving of Patent Eligibility

A. New biologics and pharmaceuticals are expensive to identify and difficult to bring to market, but relatively cheap and easy to copy

New pharmaceuticals and biologics do not simply grow on trees, ready to be picked like leaves, branches, and fruits, but instead require extensive research and development and costly trial and error. Researchers often screen thousands of candidates before identifying even a single compound, only to have a low probability of ever making it to market. Discovery of new biologics is even more difficult. Compared to pharmaceutical companies, the typical biotechnology company is smaller and more R&D-focused, has few internal revenue streams, and often relies solely on debt and private equity for funding. *See generally* Joseph A. Golec & John A. Vernon, *Financial Risk in the Biotechnology Industry*, Nat'l Bureau of Econ. Research, Working Paper No. 13604 (2007), http://www.nber.org/papers/w13604. As a result, "biotechnology firms face greater financial risk, and their R&D portfolios [are] even more sensitive to exposure to political and regulatory risk." *Id.* at 13.

The costs of developing new drugs and biologics is therefore staggering, averaging in excess of $400 million per approved drug as of 2002. John V. Duca & Mine K.

Yücel, *An Overview of Science and Cents: Exploring the Economics of Biotechnology,* 1 Fed. Res. Bank of Dallas Econ. & Fin. Pol'y Rev., no. 3, 2002, 4-5, *available at* http://www.dallasfed.org/assets/documents/research/efpr/v01_n03_a01.pdf. In contrast, the costs of imitation in these industries is low:

> The economics of developing new drugs differs from that of developing generic versions of existing drugs. First, the out-of-pocket costs of developing a generic are only $1 million to $2 million, far below the $400 million for developing a new drug. Second, the clinical success rate for generics is 90 to 100 percent, four to five times that of new drugs. Finally, it takes only one to two years to develop a generic versus ten to twelve years for a new drug.

Id. Patents covering naturally occurring compounds, such as the isolated nucleic acids at issue in this case, are an important part of this equation. Of 1010 new chemical entities approved for use by the Food & Drug Administration between 1981 and 2006, 399 are either biologics, natural products, or derived from natural products. David Newman & Gordon Cragg, *Natural Products as Sources of New Drugs Over the Last 25 Years,* 70 J. Nat. Prods. 461,463, tbl. 1 (2007). For biotechnology firms, these patents "are often the most crucial asset they own in a sector that is extremely research-intensive and with low imitation costs." Esteban Burrone, *Patents at the Core: the Biotech Business,* World Intellectual Prop. Org. (2006) (*available at* http://www.wipo.int/sme/en/documents/patents_biotech.htm).

Some amici have suggested that patents on isolated or purified products of nature prevent or deter future research. The opposite is true. Given the high "innovation costs" and low "imitation costs", there is little market incentive to be an innovator, because others can enter the market at a fraction of the cost and time. Strong patent protections therefore are critical to spur innovation:

> Mansfield (1986) sampled 100 firms in 12 U.S. manufacturing industries regarding their views of whether patents are important in making their decisions about investment in innovation. His results suggested that only in the pharmaceutical and chemical industries were patents considered essential, in the sense that more than 30 percent of their inventions would not have been developed in the absence of potential protection. In these sectors, fixed costs of R&D are high and imitation is fairly easy.

Keith E. Maskus, *Intellectual Property Rights in the Global Economy* 43 (Inst. for Int'l Econ 2000). Therefore, biotechnology and pharmaceutical companies must be able to obtain strong patent portfolios to justify their investment and risk. The USPTO's policy of granting patents on "isolated" products of nature fills this need without withdrawing subject matter that is already in the public commons.

B. Biotechnology companies are highly sensitive to changes in regulatory policy, including patent policy

The Solicitor now appears to be reversing policy, arguing in favor of a "Magic Microscope" test which would effectively remove all but "cDNA" type nucleic acid claims from patent-eligible subject matter.

This sudden change in policy threatens the viability of many biotechnology companies. Biotechnology companies are highly dependent on their patent portfolios for survival:

> Unlike companies in many other industries, biotechnology companies do not gain competitive advantages based on their ability to manufacture a product more quickly, easily, or cheaply than their competitors. Instead, biotechnology companies exert a competitive advantage by virtue of exclusive intellectual property rights granted to them by the United States and foreign governments for their discoveries. The key intellectual property right relied on by biotech companies is the utility patent, which grants its owner the right to exclude others from practicing its patented invention for a limited period of time. Owing to their reliance on patents, biotechnology companies have a greater sensitivity to changes and developments in patent law than do many other industries.

James H. Davis & Michele M. Wales, *The Effect of Intellectual Property on the Biotechnology Industry*, 50

ADVANCES IN GENETICS 427, 428 (2003). Additionally, the biotechnology industry is highly sensitive to regulatory events:

> Given the biotechnology industry's rapidly expanding role and contribution to the discovery and development of new drugs and biologics, it is important for policy makers to be cognizant of the fact that this industry, as a result of its dependence on external capital and the heightened sensitivity it has to policy shocks and new regulations, is more fragile with respect to its R&D projects and programs than the more established pharmaceutical industry. This is particular true for smallest biotechnology companies.

Golec & Vernon, *Financial Risk in the Biotechnology Industry*, Nat'l Bureau of Econ. Research, Working Paper No. 13604 (2007). Simply put, many biotechnology companies will not survive if the Court were to decide that isolated products of nature are not patent-eligible.

The Solicitor's reversal of policy – which was not joined by the USPTO – should be looked at with a skeptical eye. Patent-eligibility of isolated nucleic acids has been the status quo for at least the last 30 years. For over a decade, the official policy of the executive branch has been that claims limited to "isolated" or "purified" products of nature satisfy 35 U.S.C. § 101. *See generally* 66 Fed. Reg. 1092 (Jan. 5, 2001). Congress is well aware of this practice, having required the USPTO to "conduct a study on effective ways to provide independent, confirming genetic diagnostic test activity where gene patents and exclusive licensing for primary genetic diagnostic tests exist." Leahy-Smith America Invents Act, Pub. L. No. 112–29, § 27, 125 Stat. 283, 338 (2011) (emphasis added). Despite amending the statute to explicitly exclude inventions directed to human organisms, Congress has not amended the statute to exclude isolated nucleic acids from patentability. *Id.* at § 33, 125 Stat. at 340. Any deference afforded to the Solicitor's opinion in this case is therefore undermined by decades of inaction by the executive and legislative branches.

The Court therefore should consider the damage that will be caused to the biotechnology industry before upsetting the settled expectations of the patenting community. *Festo Corp. v. Shoketsu Kinzoku Kagyo Kabushki Co.*, 535 U.S. 722, 739 (2002); *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 32 n.6 (1997).

CONCLUSION

For the reasons stated above, Immatics respectfully requests that the Court affirm the judgment of the Federal Circuit.

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AMICUS
CURIAE
BRIEF

No. 12-398

IN THE
Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,
Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,
Respondents.

**On Writ of Certiorari to the
United States Court of Appeals
for the Federal Circuit**

BRIEF FOR INHOUSE PATENT COUNSEL, LLC AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENTS

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INTEREST OF AMICUS CURIAE

InHouse Patent Counsel LLC ("IHPC") submits this brief in support of Respondents in an effort to provide the Court with perspective from the genomics industry on the importance of gene-based patents to biotechnology companies and the patients they serve, particularly with regard to the example of Human Genome Sciences, Inc. ("HGS") of Rockville, Maryland, a company that was a leader in the discovery of human genes.[1]

From its founding in 1992 until its acquisition in 2012, HGS was a biopharmaceutical company dedicated to the discovery, development, manufacture and marketing of innovative drug products for patients with unmet medical needs. HGS researchers explored the human genome to identify and isolate novel DNA and protein targets to develop useful treatments for human disease. Like many start-up biotechnology companies, much of the funding that made HGS' research and development possible was obtained on the basis that patents would protect its human gene-based discoveries. Those investments led to important new therapies for patients, such as Benlysta®, the first new drug approved for the treatment of lupus in more than 50 years. Without the protections offered by gene patents, the life-changing products developed by HGS would not currently exist, and it is likely that many fewer such products will be developed by others in the future.

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[1] Pursuant to this Court's Rule 37.6, Amicus affirms that no counsel for a party authored this brief in whole or in part, that no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief, and that no person or persons other than amicus and its counsel made such a monetary contribution. Petitioners' consent to the filing of all amicus briefs is on file with the Clerk's office. Respondents' consent to the filing of this brief was obtained from respondents' counsel on March 13, 2013 by e-mail correspondence, a copy of which accompanies this brief.

As leaders and in-house counsel for HGS since the mid-1990s, we helped HGS develop its gene-based patent portfolio, which at one time included applications directed to more than 10,000 human genes and resulted in nearly 700 issued U.S. patents. HGS' patent portfolio was recognized in 2010 as one of the industry's top three portfolios in the Patent Board's Biotechnology Patent Scorecard. HGS understood the strength of its portfolio, and HGS' goal was always to utilize that strength to bring new and better medicines based on human genes, proteins and antibodies to patients while balancing its interests with those of the broader scientific community. HGS' portfolio enabled HGS and its partners to bring two important drugs to the market, thus providing doctors with important new treatment options for both lupus and anthrax infection. Another drug is awaiting regulatory approval and a fourth is near the end of lengthy clinical trials.

HGS was acquired in August 2012 by GlaxoSmithKline ("GSK") for $3.6 billion dollars. We are no longer affiliated with HGS (or GSK), and HGS no longer exists as an independent company. But all that HGS achieved would not have been possible had it not been able to patent its human gene discoveries.

SUMMARY OF ARGUMENT

The present appeal relates to the patent-eligibility of DNA, particularly isolated human DNA. While the parties and other amici have focused on the legal analysis of the question presented to the Court, less attention has been paid to the practical experience of companies other than Myriad with gene patents. For this reason, we write to offer the Court additional perspective on both the importance of gene patents to biotechnology companies and the positive impact that companies holding such patents can have on further scientific research using human genes.

Failing to uphold the many issued U.S. patents directed to isolated human genes would have a dramatic negative effect on the biotechnology industry and its ability to fund the discovery and development of new treatments for serious unmet medical needs. Such patents were integral to HGS' foundation and success in developing new drugs, such as Benlysta®, the first new treatment for the autoimmune disease lupus in more than fifty years. Over its twenty-year history, HGS obtained hundreds of U.S. patents covering genes, proteins, antibodies and related proprietary technologies. Those patents enabled HGS to generate funding and form strategic partnerships, without which the development of Benlysta could not have occurred.

As a practical matter, without gene patents, innovative biotechnology companies like HGS would be crippled in their efforts to raise the money needed to develop new life-saving and life-enhancing therapies. Past experience has shown that calling the patentability of such inventions into question has a strong negative influence on the investment community and can erase billions of dollars of market capitalization.

Moreover, HGS' practical experience interacting with academia over its twenty-year history demonstrates that even companies with an extensive portfolio of gene patents can encourage, rather than chill, further scientific research. Such gene patents are due to expire in the near term in any event, which calls into question the need for rebalancing the patent system to address the specter of a negative effect on scientific research that will soon be moot.

ARGUMENT

I. FAILURE TO UPHOLD HUMAN GENE PATENTS WILL NEGATIVELY IMPACT THE BIOTECHNOLOGY INDUSTRY

A. HGS Needed Gene Patents to Generate the Funding Necessary to Support Research and Development of New Therapies

Biotechnology companies generally start as small companies that garner initial funding through patenting basic research. For example, a company might patent the isolated DNA encoding a novel and useful protein that it has identified. Such fundamental patent claims can be used by the start-up as a basis for attracting funding that will enable research into strategies to impact the target of interest—for example, to bind the target or cause increased or decreased production of the target—in order to develop a useful therapeutic. Without the foundational DNA patents to encourage this funding, the later development would not occur. These types of start-up companies will be severely disadvantaged in their funding efforts if isolated genes were found to be excluded from patent-eligibility.

HGS is a case in point. By patenting gene-based inventions, HGS was able to attract funding from the investment community, which HGS used to develop novel therapeutic agents to address unmet medical needs and advance scientific research. Indeed, patent protection for genetic sequences was a central pillar in HGS' business model.

HGS was founded in July 1992 with initial investment from HealthCare Investment Corporation, the largest health care venture capital fund in the world. Concurrent with its founding, HGS gave a $70 million grant to The Institute for Genomic Research ("TIGR"), a non-profit organization engaged in "the elucidation of gene structure and function as a basic research tool in order to develop new methods of diagnosing and treating genetic disease." (See, *Human Genome Sciences Formed to Develop New Therapeutics From Basic Research on the Human Genome and Makes a $70 Million Grant to the Institute of Genomic Research*, PRNewswire, (July 7, 1992),
http://www.thefreelibrary.com/HUMAN+GENOME+SCIENCES+FORMED+TO+DEVELOP+NEW+THERAPEUTICS+FROM+BASIC...-a012304664.) The purpose of this grant was to fund TIGR's basic research and gene sequencing efforts in exchange for

the ability for HGS to obtain intellectual property rights for TIGR's gene-based discoveries, thus facilitating their commercialization.

HGS also quickly developed its own world-class scientific infrastructure and expertise to sequence and research the human genome. On the basis of its basic research into gene structure and function, and the expected promise of the resulting patents on gene-based inventions, HGS signed a $125 million collaboration agreement with SmithKline Beecham Corp. ("SmithKline") in May 1993. (See, *Glaxo Looks for Gene-Research Payoff on Other Drugs*, MarketWatch, (March 11, 2011, 11:38 AM), http://www.marketwatch.com/story/glaxo-expects-more-products-from-gene-research-2011-03-10.) Through this agreement, HGS granted SmithKline the right to develop and market certain health care products based on human genes discovered by HGS. This investment (one of the largest in the industry at the time and with no then-existing products being transferred), and the research that it spurred, would very likely not have occurred without the existence of gene patents. Armed with its initial collaborations and the prospect of patent protection for its gene-based inventions, HGS was able to raise $31 million in its initial public offering of December 1993 and more than $2 billion over the subsequent twenty years to fund its research and development efforts.

The work of HGS inured to the benefit of the scientific community and the public at large. Since its founding, HGS worked to develop therapies stemming from its genetic discoveries. This effort employed hundreds of scientists and technicians and resulted in, inter alia, the discovery of the B-lymphocyte stimulator protein, or BLyS, in 1996. The BLyS protein is believed to contribute to the production of "autoantibodies"—antibodies that attack and destroy the body's own healthy tissues—in lupus, a disease that afflicts 1.5 million Americans and millions more worldwide, as well as certain other autoimmune diseases. HGS applied for and obtained U.S. patents on the BLyS protein, the DNA encoding that protein, and other related compositions and methods.

HGS' patent portfolio was instrumental in attracting the investment money required to take its BLyS gene discoveries from the laboratory and bring them to market to benefit patients. The discovery of BLyS led to the development of Benlysta, a human monoclonal antibody that binds to and inhibits the biological activity of BLyS, thus decreasing the production of autoantibodies. Benlysta was the first specific treatment for lupus to be successfully developed in over fifty years. (See, *FDA Approves Benlysta to Treat Lupus, First New Lupus Drug Approved in 56 Years,* U.S. Food and Drug Administration, (March 9, 2011), http://www.fda.gov/newsevents/newsroom/pressAnnouncements/ucm246489.htm.) Reaching this point took an enormous financial investment. Benlysta had to undergo lengthy and rigorous clinical testing, culminating in two double-blind, placebo-controlled, multi-center Phase 3 trials. (See, *Id.)* Each of the two studies included nearly 900 patients at scores of clinical sites in multiple countries, with the first study lasting 52 weeks and the second lasting 76 weeks.

In March 2011, the FDA approved Benlysta for the treatment of lupus, the most significant advance in the treatment of lupus in more than half a century. (See, *Id.)* But it is very unlikely that Benlysta would have been developed without gene-based patents.

B. The Investment Community is Heavily Influenced by the Ability of the Biotechnology Industry to Secure Patent Protection

HGS learned through hard experience that the ability to obtain patents on human genes correlates closely with its investors' confidence. On February 11, 1994, the National Institutes of Health ("NIH") announced that it would not appeal the USPTO's rejection of NIH patent applications to uncharacterized gene fragment sequences. The response by HGS investors was swift and damaging: HGS' stock fell by 14.4% on the day of announcement and then an additional 7.7% the following day. (See, Bloomberg Business News, *Human Genome Stock Continues to Slide*, Baltimore Sun, (Feb 15, 1994), *available at* http://articles.baltimoresun.com/1994-02-15/business/1994046174_1_human-genome-sciences-gene-fragments-patent).

Similarly, HGS' stock tumbled by approximately 20% in March 2000, when comments by President Bill Clinton and United Kingdom Prime Minister Tony Blair suggested to the investment community that gene patents should be restricted. Nor was HGS alone; the biotechnology industry as a whole lost roughly $50 billion in market capitalization as a result of these comments. (See, Alex Berenson and Nicholas Wade, *THE MARKETS: STOCKS AND BONDS; A Call for Sharing of Research Causes Gene Stocks to Plunge*, N.Y. Times, Mar. 15, 2000.) HGS' stock price, like the rest of the biotechnology sector, rebounded when the comments were better explained.

Quite simply, patents provide an incentive for investment. Without DNA patents, neither the diagnostic tests developed by Myriad nor the lupus treatment developed by HGS might ever have come to fruition. As HGS' experience with Benlysta demonstrates, successful drug development can take more than 10 years and require more than $1.0 billion in investment. (See, Jon Entine, *FDA Balances Costs, Patient Safety in the Biologics and Personalized Medicine Revolution*, Forbes, (July 23, 2012, 12:05 AM), http://www.forbes.com/sites/jonentine/2012/07/23/fda-balances-costs-patient-safety-in-the-biologics-and-personalized-medicine-revolution-will-it-get-it-right-or-damage-the-miracle-industry/) Appellants complain about the cost of Myriad's screening tests, but absent its patents, Myriad might never have had the funding or incentives to develop the tests. Without DNA patents, the incredible advances in testing and therapeutics that have occurred in the last three decades — advances that have, unfortunately, been taken for granted because of they have become so common — would likely not have occurred, or would have occurred much more slowly.

II. HGS' PORTFOLIO ENCOURAGED, RATHER THAN DISCOURAGED, SCIENTIFIC RESEARCH

Like other biotechnology companies, HGS employed people who loved science. World-class scientists were found at all levels of the company from the lab bench to the boardroom, and excellence in science was a basic tenet of the company from the very beginning.

HGS fulfilled its commitment to science and scientific collaboration in the ensuing years. Academic scientists approached HGS throughout its twenty-year history for access to its extensive collection of human genes and gene products. In keeping with that commitment, HGS (like many other biotechnology companies) entered into hundreds of material transfer agreements and provided universities with research reagents that enabled and supported academic research around the world. These substantial contributions were acknowledged in numerous scientific journal publications reporting the scientists' subsequent work.

Moreover, at no point in HGS' history did it ever enforce its patents against academic researchers. As evidenced by its contributions of materials, HGS wanted to encourage further research on human genes so that new medical treatments could be discovered and developed to address unmet medical needs and ease patients' suffering. In addition, the cost of litigation would have far outweighed any potential recovery in damages that might be obtained from patent litigation against academic researchers.

We believe that this philosophy was (and continues to be) shared by many other genomics companies. Indeed, the dearth of patent litigation brought by genomics companies against academic researchers and institutions over two decades is telling.

Evidence of academic researchers' ability to study HGS' patented inventions can also be seen by examining academic research surrounding one of HGS' most important discoveries, the BLyS protein that led to the development of Benlysta, HGS' lupus treatment. Although HGS held numerous patents directed to BLyS, more than one thousand scientific papers have been published regarding the structure, activity and biology of the BLyS protein, most by third parties. Clearly, HGS' patents did not exert a significant chilling effect on academia.

Similarly, HGS did not pursue litigation against research tool companies, gene chip companies or diagnostic tool companies even though they were potentially making profits based on its patented inventions. Again, the cost of such litigation would have far outweighed the limited amount of damages that could have been obtained. Moreover, these companies were often enabling academic scientists to further research HGS' patented genes, research which indirectly benefited HGS as noted above. And again, we are unaware of evidence that other genomics companies were behaving differently.

These actions show that collaboration between industry and academia can go hand-in-hand with the availability of patents on human genes, and that gene patents advance research and discovery. If isolated genes are held to be excluded from patent-eligibility, however, biotechnology companies such as

HGS would be forced to reevaluate their relationships with academia and non-profit research institutes and in many cases may be tempted to rely on trade secret law to protect the value of their discoveries. The negative consequences of such actions on open sharing of scientific discoveries in the biotechnology field are clear.

III. THE MONOPOLY ON HUMAN GENE PATENTS IS NEARING EXPIRATION.

The Human Genome Project published multiple versions of the human genome in 2000-2003. With a twenty-year patent term, the majority of the human gene patents that were on file just prior to that publication will expire within the next 7-10 years. In fact, many of the human gene patents that were filed in the early to mid-1990's have already expired or abandoned.

Currently, it takes about ten years from discovery to bring a new biological therapy to market. Thus, if a company does not start clinical trials in the very near future, it is likely that any human gene patent now in force will expire *before* the company has progressed through clinical trials, obtained FDA approval and could potentially enter the marketplace.

We urge the Court to consider whether it is necessary to make dramatic and sweeping changes in rights that have existed for over 30 years to "solve" a problem that is close to being a non-issue due to the patent system's limit in granting monopolies.

CONCLUSION

The judgment of the Federal Circuit should be affirmed.

Respectfully submitted,

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AMICUS CURIAE BRIEF

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Supreme Court, U.S.
FILED
JAN 31 2013
OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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INTEREST OF THE *AMICUS CURIAE*[1]

The Institute of Professional Representatives before the European Patent Office (**epi**) came into existence pursuant to the European Patent Convention (EPC) upon provisions adopted by the Administrative Council of the European Patent Organization. These provisions also pertain to the European qualifying examination successful passing of which is a prerequisite for obtaining entitlement to act as a representative before the European Patent Office (EPO), and to the disciplinary powers exercised by the Institute over these representatives. The Institute (**epi**) being an international non-governmental public law corporation has its own by-laws and code of professional conduct.

At present, the Institute representing the community of European patent practitioners admitted to represent before the EPO comprises about 10,000 members from 38 European countries, both from industry and free profession.

epi as an organization deals primarily with the development and implications of patent law. **epi** through its Biotech Committee is at the forefront of all patent law developments in the fields of biotech and genetic engineering and has a sound expertise in this very specialized area. It also serves to advise the **epi** members and to forward the opinion of **epi** to other stakeholders and organizations. The **epi** Biotech Committee meets regularly and makes reports to the Council and Board of **epi** on all biotech related matters. The reports of the **epi** Biotech Committee are regularly published in the official journal of **epi** named "**epi** information" (copies of the reports can be seen on http://www.patentepi.com/patentepi/en/Information/epi-information.php). In addition, the **epi** Biotech Committee is frequently requested on an *ad-hoc* basis to produce reports for the **epi** President in support of biotech matters to be dealt with at the Standing Advisory Committee before the European Patent Office (SACEPO) or at other important meetings. The **epi** Biotech Committee also prepares the *amicus curiae* briefs on behalf of the **epi** President on biotech related inventions.

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[1] No party or party's counsel authored this brief in whole or in part. No party or party's counsel made a monetary contribution intended to fund the preparation or submission of this brief. No person other than the amicus curiae made a monetary contribution to its preparation or submission. Both parties in this case consented to the filing of this amicus brief in support of neither party.

SUMMARY OF THE ARGUMENT

European Patent Convention countries have implemented the EU Directive of the European Parliament and the Council on the legal protection of biotechnological inventions (EU Directive 98/44/EC). According to the EU directive, assuming that a DNA sequence is novel, the isolated substance of the DNA itself is patentable. The claims concern a molecule which has a defined chemical structure and function. The approach adopted by the EU Directive is that a nucleic acid corresponding to a complete or part of a gene, even if its structure is identical to that of a natural element, may constitute a patentable invention, if isolated from the human body or otherwise technically produced. According to Article 5(2) of the Directive the natural pre-existence of biological material alone does not constitute a patentability obstacle. The EU Directive established that no patent can cover a substance *in situ* in the human body; the patent must cover the isolated substance. Also, the industrial applicability of the isolated DNA, in other words its function, has to be disclosed in the patent application as filed. In Europe, especially before the EPO, genetic material is not seen as a special case requiring treatment different from chemical compounds and other products. Thus far, this view has been shared by the patent offices of the United States and Japan. In the opinion of **epi** there is no reason to change this view.

ARGUMENT

In accordance with the European Patent Convention (EPC) and with well-established case law of the Boards of Appeal of the European Patent Office, **epi** is of the opinion that isolated human DNA and other isolated nucleic acids represent patent-eligible subject matter. Although this issue has been in the public debate for years, the patent authorities in the OECD countries have been clear and consistent on this topic over the last couple of years. **epi** wishes to refer the Supreme Court to the Declaration dated 22 December 2009 of Professor Joseph Straus submitted in support of the Motion for Summary Judgment in the District Court by Myriad. The declarant Professor Joseph Straus is a renowned expert in IP law and has been a consultant and advisor to various European organizations including the European Patent Organization (EPO).

This Declaration of Professor Straus argues in detail a technical and legal basis in support of the patent-eligibility of isolated DNA claims under European patent law and practice. As a conclusion from a European patent perspective Professor Straus takes the position that Myriad's product claims for isolated human DNA at issue are patent-eligible.

epi herewith declares that it fully shares and endorses the opinion of Prof. Straus.

CONCLUSION

epi does not see any technical or legal reason why the Supreme Court could or should deny patent-eligibility of isolated human DNA including isolated human genes. Therefore, **epi** thinks that the Supreme Court should answer Question 1 in the affirmative.

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AMICUS
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BRIEF

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Respondents.

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**On Writ Of Certiorari To The
United States Court Of Appeals
For The Federal Circuit**

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BRIEF FOR THE INTELLECTUAL PROPERTY AMICUS BRIEF CLINIC OF THE FRANKLIN PIERCE CENTER FOR INTELLECTUAL PROPERTY AT THE UNIVERSITY OF NEW HAMPSHIRE SCHOOL OF LAW AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENTS

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INTEREST OF *AMICUS CURIAE*[1]

Amicus curiae is The Intellectual Property Amicus Brief Clinic of the Franklin Pierce Center for Intellectual Property. The Center is a part of University of New Hampshire School of Law (formerly Franklin Pierce Law Center). The Clinic was established to submit briefs for selected cases with the hopes of contributing important perspectives that might not otherwise be adequately represented. The Clinic seeks to file *amicus* briefs that will lead to the development and predictable application of intellectual property law to promote innovation and competition. This brief represents only the views of the participants in the Amicus Brief Clinic and the advisors to the clinic, and does not represent the views of the University of New Hampshire School of Law, the Franklin Pierce Center for Intellectual Property, or their faculty.

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SUMMARY OF ARGUMENT

The Court granted certiorari on the question "Are human genes patentable." However this is the wrong question for two reasons. First, the claims in the patents at issue are not directed to human genes in the human body. Instead, the claims are directed to isolated DNA. Second, whether the claims are "patentable" is not the issue in this case. Instead, the issue is limited to whether the claims are "patent eligible." As a result, the proper question is not whether human genes are patentable, but rather "Is Isolated DNA Patent Eligible?"

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[1] The petitioners have filed a letter of blanket consent to *amici* on January 2, 2013. Respondents granted consent to *amicus* on March 6, 2013, via electronic mail, a copy of which is being submitted herewith. No counsel for any party authored this brief in whole or in part, and no person or entity, other than *amici* and their counsel, made a monetary contribution intended to fund the preparation or submission of this brief.

The standard for patent eligibility is set forth in 35 U.S.C. § 101, which establishes that compositions of matter are patent eligible. The claims at issue in this case are directed to isolated DNA, which is a composition of matter. In addition, isolated DNA is not a law of nature, a natural phenomenon, or an abstract idea. Therefore, the answer to the specific question of whether isolated DNA is patent eligible subject matter is clearly yes.

The next question of whether isolated DNA is patentable is a separate question which includes the requirements of §§ 102, 103, and 112 in addition to the patent eligibility issue of § 101. This question of patentability is not before this Court on appeal.

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ARGUMENT

I. Introduction: The Court has Granted Certiorari on the Wrong Question

The Court granted certiorari on the question "Are human genes patentable." This question was presented by the petitioner, but the question is misleading with respect to the claims in this case.[2] As skilled advocates, the way the petitioner presented the question suggests the answer petitioner seeks, but the actual issue in this case does not so easily lead to the same answer. Answering the question presented by the petitioner, human genes in the human body occur in nature and are therefore not patentable. However, this is the wrong question, because this is not at issue in this case. The claims in the patents at issue are not directed to human genes in the human body, but to isolated DNA which codes for a protein. Further, the proper question is not whether such isolated DNA is patentable, but whether it is patent eligible.

II. Patentability is Different from Patent Eligibility, and Patent Eligibility is at Issue in the Present Case

In order for an invention to be patentable, the subject matter must first be deemed patent eligible. Patent eligibility is not the same as patentability.

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[2] The Court has ability to deny the formulation of the issues presented by the petitioner. *See U.S. v. Katz*, 389 U.S. 347, 350 (1967).

Rather, patent eligibility is the gateway to patentability. Patentability considers questions not only of patent eligibility but additionally considers novelty, obviousness, and adequacy of the written description. 35 U.S.C. §§ 101, 102, 103 and 112 (2012). As stated in *Application of Bergy*:

> "Achieving the ultimate goal of a patent . . . involves, to use an analogy, having the separate keys to open in succession the three doors of sections 101, 102, and 103, the last two guarding the public interest by assuring that patents are not granted which would take from the public that which it already enjoys (matters already within its knowledge whether in actual use or not) or Potentjally [sic] enjoys by reason of obviousness from knowledge which it already has."

596 F.2d 952, 960 (C.C.P.A. 1979). The present case involves only patent eligibility. *See Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303, 1324 (Fed. Cir. 2012), *cert. granted*, 133 S. Ct. 694 (2012).

Congress established the patent eligibility standard in 35 U.S.C. § 101: "Whoever invents or discovers any new and useful . . . composition of matter . . . may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101. This Court has repeatedly confirmed the broad scope of patent eligible subject matter in § 101: "[i]n choosing such expansive terms modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope." *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980)). Congress has left to other parts of the Patent Act the task of guarding the public interest by "assuring that patents are not granted which would take from the public that which it already enjoys" and assuring that inventions are adequately disclosed in return for the exclusive right granted by the patent. *Bergy*, 596 F.2d at 960; *see* 35 U.S.C. § 112 (2012).

As a general rule, patent eligibility extends "to 'include anything under the sun that is made by man.'" *Chakrabarty*, 447 U.S. at 309 (1980) (citing S.Rep.No.1979, 82d Cong., 2d Sess., 5 (1952); H.R.Rep.No.1923, 82d Cong., 2d Sess., 6 (1952)). While this seems to establish an extremely low bar for patent eligibility, the Court has carved out some exceptions to this general rule, restricting from patent eligibility "laws of nature, natural phenomena, and abstract ideas." *Diamond v. Diehr*, 250 U.S. 175, 185 (1980). Furthermore, claims which wholly preempt the use of a judicial exception are not patent eligible. *Bilski*, 130 S. Ct. at 3258 (2010) (Breyer, J., concurring). As will be discussed below, isolated DNA is not a law of nature, a natural phenomenon, nor an abstract idea; it is a composition of matter. A composition of matter is a real physical thing with physical limitations that cannot simply be ignored.

Once an invention has passed this minimal bar of patent eligibility, the invention should then be analyzed for the remaining patentability requirements of 35 U.S.C. §§ 102, 103, and 112. We urge the Court not to infuse the patent eligibility analysis with these other patentability considerations, which are better suited for consideration under these more appropriate provisions of the statute. For example, just because a claim is extremely broad does not mean that it is not directed to patent eligible subject matter.[3] These problems with claim scope are better resolved under, for example, the enablement requirement of 35 U.S.C. § 112. Claims that belong to a category of inventions that some believe are of "suspect validity" does not necessarily mean that the claim is not patent eligible at the threshold. *Bilski*, 130 S. Ct. at 3229. Validity concerns are better resolved, for example, under the standard for nonobviousness of 35 U.S.C. § 103. This is particularly true after the Court's decision in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). This decision is widely recognized as tightening the obviousness standard. *See generally* Jennifer Nock & Sreekar Gadde, *Raising the Bar for Nonobviousness: An Empirical Study of Federal Circuit Case Law Following KSR*, 20 FED. CIRCUIT B.J. 369 (2011). Just because a claim recites an old element (*e.g.*, hedging in *Bilski* – not patent eligible; the Arrhenius equation in *Diehr* – patent eligible) does not indicate that the claim is directed to patent ineligible subject matter. *See Bilski*, 130 S. Ct. at 3229; *Diehr*, 450 U.S. at 178. Questions regarding the novelty of an invention are better analyzed under 35 U.S.C. § 102.

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[3] This is analogous to the Court's recognition that: "Broad general language is not necessarily ambiguous when congressional objectives require broad terms." *Chakrabarty*, 447 U.S. at 315.

The Court's recent decision in *Mayo v. Prometheus* states that to be patent eligible, a method claim including a law of nature must include "additional features that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself." *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1297 (2012). The Court recognized that in evaluating additional method steps to determine whether they add such additional features, "the §101 patent-eligibility inquiry and, say, the §102 novelty inquiry might sometimes overlap." *Id.* at 1304. The claims that are currently before the court, however, are not method claims, nor (as will be argued below) are they directed to laws of nature or natural phenomena. Thus, the Court's decision in *Mayo v. Prometheus* is inapplicable to the claims at issue. The isolated DNA to which the claims are directed are compositions of matter which have been significantly altered from their naturally occurring forms. The explicit limitations of the claims separate the subject matter of the claims from any natural law or natural phenomenon, and cannot be ignored.

III. The Myriad Claims are Directed to Isolated DNA, a Composition of Matter, and the Specification Specifically Defines "Isolated"

The claims in a patent describe the metes and bounds of an invention. All claims have three principal components: a preamble, a transitional phrase, and a body. One of the basic claim types is a composition of matter claim which corresponds to the composition of matter statutory category in 35 U.S.C. § 101.

The preamble is generally a short introductory phrase to frame the context of the claim. The purpose of the preamble is to "indicate the statutory class of the claim (often by implication from the words in the preamble) and to name or define the thing that is to be claimed." ROBERT C. FABER, LANDIS ON MECHANICS OF PATENT CLAIM DRAFTING § 2.4 (6th ed., release no. 8, 2012). Most patents contain more than one claim. If some of the claims are directed to different statutory classes of invention, the preambles of the claims to each statutory class will be different. JEFFREY G. SHELDON, HOW TO WRITE A PATENT APPLICATION § 7.3.3 (2nd ed., release no. 6, 2012). The transitional phrase separates the preamble from the body of the claim. The term "comprising" is the most frequently used transitional phrase. The body of the claim includes the limitations of the invention.

Composition of matter claims are used to define "all compositions of two or more substances and . . . all composite articles, whether they be results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids." *Shell Dev. Co. v. Watson*, 149 F. Supp. 279, 280 (D.D.C. 1957). As explained below, the claims at issue in this case are composition of matter claims.

IV. Isolated DNA as Defined in the Myriad Patents is a Composition of Matter and is Therefore Patent Eligible

Having established that the issue is patent eligibility, and that compositions of matter, such as isolated DNA, are generally patent eligible, the argument turns to the invention at issue: isolated DNA.

Claim 1 in Myriad's '282 patent [hereinafter Claim 1] claims "An isolated DNA coding for a BRCA1 polypeptide. . . ." U.S. Patent No. 5,747,282 col. 153 l. 56 (filed June 7, 1995). Claim 1 is representative of the claims at issue in this case. This claim and the other claims in the patents at issue are directed to isolated DNA molecules. The preamble of Claim 1 states "[a]n isolated DNA. . . ." *Id.*

In Myriad's patents at issue, "[a]n 'isolated' . . . nucleic acid . . . is one which is substantially separated from other cellular components. . . . The term embraces a nucleic acid sequence of protein which has been removed from its naturally occurring environment. . . ." U.S. Patent No. 6,033,857 (filed Mar. 20, 1998); U.S. Patent No. 5,837,492 (filed Apr. 29, 1996); U.S. Patent No. 5,753,441 (filed Jan. 5, 1996); U.S. Patent No. 5,747,282 (filed June 7, 1995); U.S.

Patent No. 5,710,001 (filed June 7, 1995); U.S. Patent No. 5,709,999 (filed June 7, 1995); U.S. Patent No. 5,693,473 (filed June 7, 1995). When a term is clearly defined in the specification of a patent, this meaning must be applied when construing the claims using that term. *Phillips v. AWH Corp.*, 415 F.3d 1303 (2005) ("the specification 'acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication"). The isolated DNA, as limited by the preamble in Myriad's claims, therefore, is DNA that has been extracted, purified, and chemically altered. Thus, the isolated DNA "constitute[s] an *a fortiori* situation, where [it is] not only purified; [it is] different from the natural products in 'name, character, and use.'" *Chakrabarty*, 447 U.S. at 309-10; *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303, 1328-29 (Fed. Cir. 2012), *cert. granted*, 133 S. Ct. 694 (2012). Unlike in *Funk Bros*, where the nematodes were not changed in any manner other than mixing of different unaltered nematodes, the isolated DNA at issue here is significantly changed from its naturally occurring form. *See Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948).

Additionally, the particular claims of Myriad's 5,837,492 patent relate to a subset of isolated DNA, as defined by Myriad's patents, known as complementary DNA, or cDNA. U.S. Patent No. 5,837,492 cols. 167-69 (filed Apr. 29, 1996) (claiming cDNA as a "replicative cloning vector" as defined in the specification). As explained in the prior Federal Circuit decision:

> cDNA is synthesized from mRNA using complementary base pairing in a manner analogous to RNA transcription. . . . Because it is synthesized from mRNA, cDNA contains only the exon sequences, and thus none of the intron sequences, from a chromosomal gene sequence.

Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office, 689 F.3d at 1313-14. The claimed cDNA is an invention that is made by man as was the microorganism made by Chakrabarty. *See Chakrabarty*, 447 U.S. 303.

Substances that have been isolated from naturally occurring sources are "new" under 35 U.S.C. § 101 when the resulting substance is substantially different from the naturally existing source. *Id.* at 310. This must be true, for § 101 specifically grants patent eligibility to compositions of matter, and all matter is made completely of known atoms and derived from naturally existing materials. 35 U.S.C. § 101 (2012). What matters for issues of patent eligibility is the specific structure of the compound claimed. In the patents at issue, the specific claimed structures are particular isolated DNA sequences.

At no point during a cell's natural lifecycle are sequences isolated in the manner claimed by Myriad.[4]

As noted in other *amicus* briefs, it is possible for the random process of DNA fragmentation following cell death to result in a DNA fragment with any sequence. *See, e.g.*, Brief for Eric S. Lander as Amicus Curiae in Support of Neither Party, *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 689 F.3d 1303 (Fed. Cir. 2012), *appeal docketed*, No. 12-398 (U.S.

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[4] While long chain DNA exists in nature, it exists in a highly organized structure, and is generally only dissolved upon cell death. The primary purpose of long chain DNA is the storage of genetic information to serve as a set of instructions for protein generation. An analogy to construction may be helpful. When proteins are built by cells, DNA serves as the architect; its base pairs interact with RNA polymerase to create mRNA, the blueprint. RNA polymerase "unzips" the native DNA's double-helix structure by temporarily breaking the hydrogen bonds connecting the strands, creating the mRNA through breaking the hydrogen bonds connecting the strands, creating the mRNA through use of base-pair association with the strand of DNA it is attached to. As RNA polymerase moves along the DNA strand, the DNA "rezips" back into its original structure. Upon reaching a transcription terminator, the RNA polymerase disengages from the DNA, leaving the DNA fully reassembled, and releasing the completed mRNA into the cell. It is from this mRNA "blueprint" that proteins are created. Through this entire process, the gene region on the DNA strand remains bound to the rest of the DNA. Due to the substitution of uracil in RNA for the thymine bases in DNA, RNA is not interchangeable with DNA, thus, isolated DNA is not found in this process. *See generally Animation: mRNA Synthesis*, McGRAW-HILL, http://highered.mcgraw-hill.com/sites/0072507470/student_view0/chapter3/animation__mrna_synthesis__transcription___quiz_1_.html (last visited Mar. 9, 2013).

Sept. 25, 2012), 2013 WL 432959. However, the claims must be read in light of the specification. 37 C.F.R. § 1.75(d)(1) (2012). As previously stated, the specifications at issue all define "isolated" as "substantially separated from other cellular components." U.S. Patent No. 5,747,282 col. 19 ll. 8-18 (filed June 7, 1995). Therefore, any DNA fragments that may result from this process are still not "isolated" DNA as defined in the specifications.

Because isolated DNA must be obtained through laboratory techniques, it is not naturally occurring, and therefore fulfills the "new" requirement of 35 U.S.C. § 101. 35 U.S.C. § 101.

While the utility of isolated DNA is not at issue in this case, for a proper patent eligibility determination, it must be considered. 35 U.S.C. § 101; *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 694 (2012); Brief for Petitioner, *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 689 F.3d 1303 (Fed. Cir. 2012), *appeal docketed*, No. 12-398 (U.S. Sept. 25, 2012), 2012 WL 4502947. Isolated DNA has many scientifically-recognized uses, including experimental marking and testing for genetic diseases or predisposition to certain genetic diseases (as in the case of the BRCA1 and BRCA2 genes at issue here). *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 689 F.3d 1303, 1314 (Fed. Cir. 2012). With such identified man-made uses, it is clear that isolated DNA has operable and practical utility. *Juicy Whip v. Orange Bang*, 292 F.3d 728 (Fed. Cir. 2007).

As discussed above, in addition to being new and useful, it is necessary that none of the judicial exceptions to patent eligibility apply. In particular, isolated DNA is not a law of nature, a natural phenomenon, nor an abstract idea; it is a composition of matter and as such, a real, physical thing.

Abstract ideas have been repeatedly held patent-ineligible. *See, e.g., Bilski v. Kappos*, 130 S. Ct. 3218 (2010); *State St. Bank & Trust Co. v. Signature Fin. Grp., Inc.*, 149 F.3d 1368 (Fed. Cir. 1998). Unlike the inventions in any of those cases, isolated DNA is a physical, tangible thing; therefore, it cannot be abstract nor can it wholly preempt an abstract idea. Laws of nature have similarly been held not patent eligible. *See, e.g., Mayo Collaborative Servs v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012). But, unlike, for example, Einstein's famous $E=mc^2$, isolated DNA is a composition of matter, not a law of nature. Finally, although discussed in several cases, the physical phenomena exception to patent-eligibility has not been formally defined. Douglas L. Rogers, *Coding for Life – Should Any Entity Have the Exclusive Right to Use and Sell Isolated DNA?*, 12 PITTSBURGH J. TECH. L. & POL'Y 3 (2011) ("The Supreme Court has not defined 'physical phenomena' "); *see, e.g., Mayo Collaborative Servs.*, 132 S. Ct. 1289; *Bilski*, 130 S. Ct. 3218. Regardless of this lack of definition, as a composition of matter, isolated DNA should not fall into a category supposedly containing such concepts as electromagnetism or the weather. Additionally, the isolated DNA is man-made and cannot wholly preempt a natural phenomenon because the preamble to the claim is limited specifically to isolated DNA. *See* U.S. Patent No. 5,747,282 col. 19 ll. 8-18 (filed Jun. 7, 1995).

V. The Correct Question to Ask is "Is Isolated DNA Patent Eligible?"

Based on the issues presented in this case, the question the Court should be asking, and is understood to be the question the Court intended to ask, is "Are isolated DNA molecules patent eligible?" As the Federal Circuit stated in its opinion, "the issue is *patent eligibility,* not *patentability.*" *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303, 1324 (Fed. Cir. 2012), *cert. granted*, 133 S. Ct. 694 (2012) (emphasis added). The principal claims at issue relate to isolated DNA molecules, not to human genes in the human body. *See id.* at 1325.

In addition to not answering the issues in this case, there are other consequences of asking the wrong question. Asking the question presented has led to public alarm. Jonathan Stempel, *Supreme Court to Decide if Human Genes Patentable*, REUTERS (Nov. 30, 2012), http://www.reuters.com/article/2012/11/30/us-usa-court-genes-idUSBRE8AT19620121130 (last visited Mar. 10, 2013). The question presented is a "sound bite" question to raise the public interest in this case, but this case is not about patentability of human genes. *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303, 1324 (Fed.

Cir. 2012), *cert. granted*, 133 S. Ct. 694 (2012). This case is about the patent eligibility of isolated DNA molecules, not the patentability of human genes. *Id.*

Asking the broader question "are human genes patentable" has already had consequences. *Amicus* briefs in this case as well as articles in the popular patent press have already speculated on a "parade of horribles," raising public alarm. Brief for James D. Watson as Amicus Curiae in Support of Neither Party, *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 689 F.3d 1303 (Fed. Cir. 2012), *appeal docketed*, No. 12-398 (U.S. Sept. 25, 2012), 2013 WL 432951; Stempel, *supra*. A common horrible is that allowing patents on human genes would "preempt" research. The issue of whether the patents at issue in this case "preempt" or prevent scientific research is not presented by this case. Dr. Ostrer, the only plaintiff found to have standing, has never been prevented from scientific research using the isolated genes. Dr. Ostrer's assertion that: "The claims preempt any use of the genes for any purpose" is not consistent with the long standing experimental use exception to infringement. Brief for Petitioner at 2, *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 689 F.3d 1303 (Fed. Cir. 2012), *appeal docketed*, No. 12-398 (U.S. Sept. 25, 2012), 2012 WL 4502947. This exception is found in the jurisprudence of this Court and in many decisions of the Court of Appeals. *In re Rosuvastatin Calcium Patent Litigation*, 703 F.3d 511, 527 (Fed. Cir. 2012); *Classen Immunotherapies, Inc. v. Biogen IDEC*, 659 F.3d 1057 (Fed. Cir. 2011);

Whittemore v. Cutter, 29 F. Cas. 1120, 1121 (C.C.D. Mass. 1813) (No. 17,600).

Additionally, finding isolated DNA to be not patent eligible would place the United States in an awkward position with respect to international harmonization of patent law.[5] In many countries, the patent eligibility of isolated DNA is not an issue; it is patent eligible subject matter. For instance, Rule 29(2) of the EPC states that "element[s] isolated from the human body . . . including the sequences or partial sequences of a gene" are patent eligible subject matter "even if the structure of that element is identical to that of a natural element." Eur. Patent Convention Rule 29(2), *available at* http://www.epo.org/law-practice/legal-texts/html/epc/2010/e/r29.html. However, the simple discovery of the sequence of a gene itself is not patent eligible according to Rule 29(1). Eur. Patent Convention Rule 29(1), *available at* http://www.epo.org/law-practice/legal-texts/html/epc/2010/e/r29.html. As a second example, the sister case filed in Australia was recently dismissed on summary judgment because the Myriad claims were distinctly patent eligible. *Cancer Voices Australia v Myriad Genetics, Inc.* [2013] FCA 65 (Austl.).

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[5] It is noted that during the oral argument in *Bilski*, there was an inquiry about European patent law. Transcript of Oral Argument at 12-13, *Bilski v. Kappos*, 130 S. Ct. 3218 (2010) (No. 08-964).

VI. The Court Should Find That the Myriad Claims are Directed to Patent Eligible Subject Matter: Isolated DNA

Claim 1 is directed to an isolated DNA molecule. A human gene is not an isolated DNA molecule. A gene is "one of the elements of the germ plasm serving as specific transmitters of hereditary characters and usually regarded as portions of DNA linearly arranged in fixed positions and as functioning through control of the syntheses if specific polypeptide chains." WEBSTER'S THIRD NEW INTERNATIONAL DICTIONARY 944 (Philip B. Gove, et al., eds., 1993). Therefore, even if the Court answers the question "Are human genes patentable?", the result will not address the controversy presented. The claims at issue are not directed to genes and do not reference genes. The claims at issue are directed to isolated DNA molecules, as seen in the language of representative Claim 1: "An isolated DNA molecule. . . ." U.S. Patent No. 5,837,492 col. 167 l. 17 (filed Apr. 29, 1996). However, if the Court asks the question presented here "Is isolated DNA patent eligible?", then the issues presented in this case will be addressed.

◆

CONCLUSION

The Court is currently asking the wrong question. The correct question is "Is isolated DNA patent eligible?" Because isolated DNA is a product of human ingenuity and a composition of matter, we believe it to be patent eligible. Because it is understood that the Court intended to ask the question of "Is isolated DNA patent eligible?", the Court should find for Myriad. Whether isolated DNA is patentable is a separate question and is not before the court on appeal. The question of patentability includes the requirements of §§ 102, 103, and 112 in addition to the patent eligibility issue of § 101.

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AMICUS
CURIAE
BRIEF

Supreme Court, U.S.
FILED
MAR 4 2013
OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF INTELLECTUAL PROPERTY OWNERS ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENTS

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INTEREST OF THE *AMICUS CURIAE*[1]

The Intellectual Property Owners Association (IPO) is a trade association representing companies and individuals in all industries and fields of technology who own or are interested in intellectual property rights. IPO's membership includes more than 200 companies and over 12,000 individuals who are involved in the association either through their companies or as inventor, author, executive, law firm, or attorney members. Founded in 1972, IPO represents the interests of all owners of intellectual property. IPO regularly represents the interests of its members before Congress and the USPTO and has filed amicus curiae briefs in this Court and other courts on significant issues of intellectual property law. The filing of this brief was approved by the IPO Board of Directors. A list of the IPO board members can be found in the Appendix.[2]

SUMMARY OF THE ARGUMENT

Isolated human genes[3], particularly genetically-engineered embodiments thereof, are patent-eligible subject matter under the Patent Act (35 U.S.C. § 101) and controlling Supreme Court precedent. *Diamond v. Chakrabarty*, 447 U.S. 303 (1980). Claims directed to isolated human DNA show "the hand of man" and are "not nature's handiwork, but [the inventors'] own," the fundamental requirement of patent-eligibility for composition claims. While derived from nature, the processes involved in isolating human DNA alter the chemical structure of these molecules in profound and fundamental ways, converting them into forms that never existed prior to their isolation.

---

[1] No party's counsel authored this brief in whole or part; no party or party's counsel contributed money intended to fund preparing or submitting the brief; and no person other than *amicus*, its members, or counsel contributed money intended to fund preparing or submitting the brief. Counsel for all parties have consented to the filing of this brief.

[2] IPO procedures require approval of positions in briefs by a two-thirds majority of directors present and voting.

[3] While Petitioners and their *amici* provocatively refer to the subject matter at issue in this case as "human gene patenting," this term inaccurately characterizes the claims in Myriad's patent. Instead, what is claimed is a specific sequence of isolated human DNA.

Patenting isolated human DNA is consistent with constitutional provisions defining the powers of Congress, as patenting isolated human DNA "promotes the progress of . . . the Useful Arts" by incentivizing disclosure of genetic information, which is not patentable subject matter *per se*. Such patenting does not inhibit scientific research, as evidenced by the thousands of scientific journal articles published and research grants obtained after patenting of the two breast cancer-related genes (BRCA1 and BRCA2) that are the subject of this lawsuit. Patents and the assertion of patents are related to commercial not basic research activities, and the overwhelming evidence of several studies is that patents on isolated human DNA have had no effect on basic scientific research.

Petitioners fatally overreach in asking this court to hold that isolated human DNA falls outside the scope of patent-eligible subject matter. The patents at issue, directed to isolated human DNA encoding BRCA1 and BRCA2, represent only the beginning of an era of personalized medicine that will be characterized by understanding, and utilizing, genetic differences that impact both an individual's propensity for succumbing to diseases and disorders as well as making a determination of the best therapeutic interventions and treatments for addressing them. Patents in this area are needed to promote expeditious disclosure of the genetic bases for such diagnostic and therapeutic approaches to human disease; without them, alternative means of protecting such discoveries, *for example* by holding them as trade secrets, will become more attractive. Patent-eligibility of isolated human DNA promotes not only disclosure of the DNA itself (and the proteins encoded thereby) but also the best mode for making and using the isolated human DNA and related methods. Even should the basic genetic information be available elsewhere, failure to patent also means failure to require full disclosure, and the attendant suppression of information would affect the development of reliable drugs and diagnostic methods (or worse, permit private companies to hold such information indefinitely). Such an outcome would be adverse to the public interest and contrary to the sound public policy underlying the Patent Act.

Petitioners wrongly equate patenting of isolated human DNA with patenting genetic information. This equation is false: genetic information is not patentable subject matter *per se*. It is available on public databases, both governmental (patent) and private, throughout the world, and is freely available for genetic research. Patenting isolated human DNA not only does not impact an individual's genetic information, it promotes progress in genetic research by requiring applicants to disclose what they know about the best mode of making and using said isolated human DNA. Moreover, patenting isolated human DNA promotes the elucidation of the identities and functions of the thousands of heretofore unrecognized genes found by researchers involved in the

Human Genome Project. Patents provide the incentive to invest the time, money, and manpower to understand what these genes encode and what the encoded proteins do, both being requirements imposed under 35 U.S.C. § 101 as interpreted by the U.S. Patent and Trademark Office.

All these benefits fall squarely within the ambit of the basis for Congress's power to grant patents, to "Promote the Progress . . . of the Useful Arts." For that reason alone this Court should affirm the Court of Appeals decision below.

ARGUMENT

I. Isolated Human DNA is Patent-Eligible Subject Matter

This Court has recognized that patent eligibility should be given an expansive scope, as mandated by Congress under 35 U.S.C. § 101. In *Diamond v. Chakrabarty*, this Court noted that Congress' intent was for statutory subject matter to "include anything under the sun that is made by man," (447 U.S. 303, 309 (1980) (quoting S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952); H.R. Rep. No. 1923, 82d Cong., 2d Sess., 6 (1952))), consistent with Thomas Jefferson's vision that "ingenuity should receive a liberal encouragement," *Id.* at 308 (quoting 5 Writings of Thomas Jefferson 75–76 (Washington ed. 1871)).

The Patent Act defines four classes of inventions that are eligible for patenting: machines, processes, manufactures, and compositions of matter. 35 U.S.C. § 101. This Court has spoken with great clarity on the scope of the "manufacture" and "composition of matter" classes in *Diamond v. Chakrabarty*:

> [T]his Court has read the term "manufacture" in § 101 in accordance with its dictionary definition to mean "the production of articles for use from raw or prepared materials by giving to these materials new forms, qualities, properties, or combinations, whether by hand-labor or by machinery."

447 U.S. 303, 308 (1980) (quoting *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1, 11 (1931)). This Court gave an equally expansive reading to the class "composition of matter":

> "[C]omposition of matter" has been construed consistent with its common usage to include "all compositions of two or more substances and . . . all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids."

Id. (quoting *Shell Development Co. v. Watson*, 149 F.Supp. 279, 280 (D.D.C. 1957)).

This Court fashioned a straightforward test of whether a manufacture or composition of matter was patent-eligible: it must demonstrate the "hand of man," something that is "a product of human ingenuity 'having a distinctive name, character [and] use.'" *Id.* at 309–10 (citing *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887)). The Court distinguished the holding in *Funk Brothers Seed Co.* in this regard, where the patentee had discovered only "some handiwork of nature" and thus had discovered something that was not patent-eligible. *Id.* at 10. The Court's *Chakrabarty* test is the proper standard for patent-eligibility, not the imposition of bright line, categorical rules applying broad, categorical prohibitions such as that advanced by Plaintiffs and their *amici*. *Anything* that evinces the "hand of man" is patent-eligible.

A. Isolated Human DNA is Patent-Eligible Because it Satisfies These Requirements Set Forth in *Chakrabarty*

Myriad's claims are narrowly focused on isolated human DNA molecules that encode a protein having a particular amino acid sequence. For example, claim 1 of Myriad's U.S. Patent No. 5,837,492 states:

> An *isolated* DNA molecule *coding for* a BRCA2 polypeptide, said DNA molecule comprising a *nucleic acid sequence* encoding the amino acid sequence set forth in *SEQ ID NO:2*.

Since the claimed inventions at issue here are directed to chemical molecules that do not occur in nature, they qualify as both "manufactures" and "compositions of matter." Therefore, *Chakrabarty* is the controlling precedent for determining whether Myriad's claims are drawn to patentable subject matter.

Isolated human DNA is patent-eligible because it satisfies the requirement in *Chakrabarty* that claimed subject matter show "the hand of man." The claimed isolated human DNA does this in several ways.

The claimed human DNA encoding BRCA1 and BRCA2 is isolated human DNA – the claims do not encompass the genes present in any cell. *See* Utility Examination Guidelines, 66 Fed. Reg. 1092, 1093 (Jan.

5, 2001). Thus, a patent on isolated human DNA does not implicate any individual's right to her own genes, since an individual's genes fall outside the scope of the patent claim. Indeed, these claims would not even encompass a recombinant cell containing a copy of either of the isolated human DNAs as claimed, since in that case the human DNA would not be "isolated."

It is important to recognize what "isolating" human DNA and encoding a protein entails. Genes are present in cellular DNA, which in humans is organized into 46 chromosomes; the entire genetic complement (or genome) in the cell comprises about six billion nucleotides of DNA.[4] An individual gene typically comprises about 1,000 of these nucleotides. Thus, to isolate a gene requires these specific 1,000 nucleotides to be separated from the remaining (approximately) 5,999,999,000 nucleotides in the cellular genome. Isolated human DNAs for each species (BRCA1 and BCRA2) have distinct nucleotide sequences and particular physical and chemical properties that distinguish them from all other DNA sequences.[5]

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[4] A useful primer on the basics of molecular biology can be found in *In re O'Farrell*, 853 F.2d 894, 895-900 (Fed. Cir. 1988).

[5] Genes in human chromosomal DNA, including the BRCA1 and BRCA2 genes at issue here, are not neatly arrayed in the chromosome, but are separated by unrelated DNA. The nucleotide sequence of a gene encodes a protein, and the gene is used by the cell as a "chemical blueprint" for making the protein. In this process, the portions of the gene that encode a protein (called "exons") are separated by unrelated portions of DNA (called "introns"). The cell produces a messenger RNA (mRNA) copy of the gene that removes the introns from the copy; it is this mRNA that is used to produce the protein by a cellular process called "translation." It is also the mRNA copy that can be used to isolate human DNA encoding specific proteins having specific amino acid

Claims to isolated human DNA, including isolated human DNA encoding BRCA1 and BRCA2, encompass in some embodiments DNA copies of mRNA.[6] These copies are termed "complementary DNA" or "cDNA" copies, and are the product of an enzymatic conversion of the mRNA to cDNA by a viral enzyme called reverse transcriptase. This enzyme is not present in cells that have not been infected by a virus that produces the enzyme, and cDNA copies of mRNAs encoding isolated human DNA, including isolated human DNA corresponding to BRCA1 and BRCA2, do not exist without human intervention, *i.e.*, prior to their synthesis by a researcher.

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sequences. Thus, in certain embodiments, claims to isolated human DNA, including the isolated human DNA encoding BRCA1 and BRCA2 at issue here, are copies not of the chromosomal DNA but of the mRNA.

[6] RNA (including mRNA) and DNA are distinct molecules that differ structurally and functionally. As the names imply, the molecules are different chemically, DNA comprising *deoxyribose* and RNA comprising *ribose*; these chemical differences are reflected in differences in stability and resistance to degradation. Also, DNA (generally) exists as a "double helix," wherein each molecule comprises two strands wound about each other. The nucleotide sequence on each strand is complementary to the other strand, as found by Watson and Crick as the basis for DNA being the genetic material. RNA, on the other hand, is single-stranded, and contains the nucleotide sequence from only one of the strands of the DNA double helix. The two types of molecules also exhibit a variety of other physical and chemical differences. While every human cell contains two copies of the BRCA1 and BRCA2 genes (and almost every other gene), not all cells express these genes, *i.e.*, make the mRNA that is the starting point for isolating the gene. Thus, the inventor must identify such a cell before human DNA corresponding to the gene can be isolated.

It is not merely that these cDNAs are new (which is a question of patentability rather than patent-eligibility), but that they are a "nonnaturally occurring manufacture or composition of matter - a product of human ingenuity." *Chakrabarty*, 447 U.S. at 309. Like Chakrabarty's bacterium, isolated human DNA, and specifically the isolated human DNA encoding BRCA1 and BRCA2 claimed in the patents-in-suit, are "not nature's handiwork, but [the inventors'] own," and thus are eligible for patenting under Supreme Court precedent. *Id.*

The above characteristics of claimed isolated human DNA, including the isolated human BRCA1 and BRCA2 DNA, demonstrate that claimed isolated human DNA satisfies the requirements of *Chakrabarty* that patent-eligible subject matter show "the hand of man."

B. There is no Precedent that Controverts *Chakrabarty*

While the Court has recognized that the scope of patent-eligible subject matter is not infinite, it has been parsimonious in setting forth what was not patent-eligible. "[L]aws of nature, physical phenomena, and abstract ideas" fall into this category, which the Court exemplified as "a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter." *Chakrabarty*, 447 U.S. at 309. Similarly, this Court has said that "[l]ikewise, Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity." *Id.*

These proscriptions against patent eligibility have been most recently revisited by this Court in *Mayo*

Collaborative Services v. Prometheus Labs., Inc.. 132 S. Ct. 1289, 1294 (2012). In *Mayo*, the claims were directed to a natural law relating to the proper therapeutic dosage of a drug for treating Crohn's disease. In finding the claim ineligible for patenting, this Court said that

> [t]he claims purport to apply natural laws describing the relationships between the concentration in the blood of certain thiopurine metabolites and the likelihood that the drug dosage will be ineffective or induce harmful side-effects. We must determine whether the claimed processes have transformed these unpatentable natural laws into patent eligible applications of those laws. We conclude that they have not done so and that therefore the processes are not patentable.

Id. The deficiency in the claim was that it did no more than "inform a relevant audience about certain laws of nature," and "any additional steps [recited in the claim] consist of well understood, routine, conventional activity already engaged in by the scientific community." *Id.* at 1298. Accordingly, "those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately" and thus the claimed method was unpatentable. *Id.*

As expressed by the *Mayo* Court, these concerns arise when the claims produce no more than information (inform a relevant audience about certain laws of nature). *Id.* Indeed, *Mayo* is simply the latest in a series of such decisions dating back 160 years. This Court has addressed this type of deficiency in *O'Reilly v. Morse*, 56 U.S. 62, 62 (1853), claiming a method of transmitting information using electromagnetism; *Gottschalk v. Benson*, 409 U.S. 63, 64 (1972), claiming methods for converting binary-coded decimal (BCD) numerals into pure binary numerals on a general purpose digital computer using a particular algorithm; *Parker v. Flook*, 437 U.S. 584, 585 (1978), claiming methods for determining an alarm limit; and *Bilski v. Kappos*, 130 S. Ct. 3218, 3224 (2010), claiming methods for hedging commodity trading outcomes. In each of these decisions, the Court found a lack of patentable subject matter because the claimed method provided little (or nothing) more than abstract information as opposed to concrete inventions that "promote the Progress of ... the useful Arts." U.S. Const. art. I, § 8, cl. 8.

This Court has been wary of claims that preempt all uses of a law of nature, as it deemed them to be in *Mayo*, *Benson*, *Flook* and *Bilski*. In *Mayo*, the Court warned that "upholding the patents would risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries" and would "threaten to inhibit the development of more refined treatment recommendations (like that embodied in Mayo's test), that combine Prometheus' correlations with later discovered features of metabolites, human physiology or individual patient characteristics." *Mayo*, 132 S. Ct. at 1294, 1302. These statements illustrate this Court's continuing concern that laws of nature are "'manifestations of . . . nature, free to all men and reserved exclusively to none'"; *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948).

The Court's decision in *Diehr* illuminates the boundaries of the Court's concern with preemption. In

Diehr, a method for curing rubber using an application of the Arrhenius equation was deemed patent-eligible. 450 U.S. 175, 177 (1981). There, the production of a tangible outcome -- using the claimed method to make cured rubber -- distinguishes the patent-eligible claims from the information produced in the claimed methods deemed patent-ineligible by this Court. And because the claims in *Diehr* were drawn to a specific method of making cured rubber,this Court found that the claim did not preempt all uses of the Arrhenius equation.

Unlike the method claims in *Mayo*, *Benson*, *Flook* and *Bilski*, Myriad's composition of matter claims at issue here are not broadly preemptive. They are both specific and concrete and as such do not implicate the policy concerns enunciated by this Court in those cases where preemption rendered claims patient-ineligible. Rather than being directed to mere information, the claims at issue are drawn to a useful and concrete composition of matter that falls within the statutory classes of patentable subject matter defined by Congress in Section 101 of the patent statute. Since Myriad's claimed inventions "evince the hand of man," they are directed to patentable subject matter per *Chakrabarty*.

Particularly relevant to the question of preemption is the narrow scope of Myriad's claim. The only isolated (human) DNA molecules that fall within the literal scope of this claim are those that encode the precise amino acid sequence called out in the claim. An isolated human DNA that is changed in any way from the specifically claimed amino acid sequence can be performed freely without literal infringement liability by anyone.[7] Indeed, such claims to isolated human DNA are the antithesis of the type of broadly preemptive claims that have concerned this Court in the past, because by their nature these narrow claims do not "impede the flow of information that might permit, indeed spur, invention." *Mayo*, 132 S. Ct. at 1305.

Moreover, disclosure as required by the Patent Act is "the *quid pro quo* of the right to exclude." *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 484 (1974). The Federal Circuit has interpreted 35 U.S.C. § 112 to require that claims to isolated human DNA must disclose the specific sequence claimed (or provide a biological deposit thereof). *See Board of Trustees of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997); *Ariad Pharma. Inc. v. Eli Lilly & Co.*, 598 F.3d 1336 (2010) (*en banc*). In addition, the U.S. Patent and Trademark Office has implemented these requirements. *See* USPTO Written Description Examination Guidelines, 66 Fed. Reg. 1092 (2001). By requiring such a detailed disclosure for isolated DNA claims, the public is provided with a fair and balanced *quid pro quo* for the narrow patent grant given the inventors. And in this case, Myriad's disclosure of the

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[7] The significance of this limitation in scope of Myriad's claims can be understood by the following: if the single change in the amino acid sequence of the BRCA2 protein encoded by the claimed isolated human DNA is from a valine (Val) residue to an isoleucine (Ile) residue, the number of atoms in the protein is increased by a mere 3 atoms (the difference in structure between these two amino acids is a methylene group,-CH_2-) out a total of more than *60,000* atoms in the protein. Yet, even such a small change means that the altered molecule does *not* literally infringe claim 1 of Myriad's '492 patent.

BRCA1 and BRCA2 gene sequence has provided current and future researchers with the ability to continue to research and alter and make improvements in the BRCA1 and BRCA2 genes.

None of the cases asserted by Plaintiffs or their *amici* counters this Court's clear precedent in *Chakrabarty*.[8] On the contrary, the correct interpretation of each of these cases is consistent with patent-eligible subject compositions of matter having but one requirement -- that it show "the hand of man."

For example, *American Wood-Paper Co. v. Fibre Disintegrating*, 90 U.S. 566 (1874) ("*The Wood-Paper Patent Cases*"), which involved claims for the product of a method for making paper from wood pulp, held that claims to *prior art* compounds could not be made patentable merely by isolating them. The Court's concern was not to define categories of subject matter that are *per se* patent-ineligible, but rather that a patentee not be permitted to withdraw from the public domain subject matter that had been previously freely available for public use. *Id.* at 594–95 Indeed, the Court expressly declined to decide whether purification could convert a compound present in an impure state into a patent-eligible purified compound as the product of a process. *Id.*

The same infirmities arose in the patents at issue in *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293

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[8] Plaintiffs or their *amici* cite several cases from lower courts regarding what they allege are "natural products" and that purportedly show the unpatentability thereof. These cases do not represent this Court's precedent; indeed, the only direct authority that speaks to the question before this Court is *Chakrabarty*.

(1884), where the patents disclosed methods for preparing a dye, alizarine, and the product of such methods. The Court found that what the disclosed process produced was "the substance already known as alizarine," and the Court found claims to "artificial alizarine" were not patentable because what was claimed was something that was already known:

> According to the description in [the patents in suit], and the evidence, the article produced by the process described was the alizarine of madder, having the chemical formula $C_{14}H_8O_4$. It was an old article. While a new process for producing it was patentable, the product itself could not be patented, even though it was a product made artificially for the first time, in contradistinction to being eliminated from the madder root. Calling it artificial alizarine did not make it a new composition of matter, and patentable as such, by reason of its having been prepared artificially, for the first time, from anthracine, if it was set forth as alizarine, a well-known substance. *Wood Paper Patent*, 23 Wall. 566, 593. There was therefore no foundation for reissue No. 4,321, for the product, because, on the description given, no patent for the product could have been taken out originally.

Id. at 301–12. It is clear that the Court was not rendering a decision on patentable subject matter, but was instead applying the principle that a patentee cannot remove a known article from the public domain merely by providing a new way of making that old article.

In *Funk Brothers Seed Co.* the Court held unpatentable an article of manufacture comprising a mixture of two types of nitrogen-fixing bacteria, in a context where the bacteria were known in the art, and also known to fall into six well-defined groups that could not be cultivated together (they exhibited growth inhibition when grown in mixed culture).[9] The Court said that it had "long been well known" to produce cultures of these bacteria in the laboratory and provide farmers with such cultures for inoculating leguminous plant seeds, and also that the properties of the different bacterial species, their capacity to infect different plants, and their growth inhibition were known in the art. *Funk Bros. Seed Co.*, 333 U.S. at 129. Under these circumstances, the Court held that claims to the co-cultures were unpatentable. *Id.* at 130. These concerns echo the statements of this Court in *Mayo*, that the steps of the method there disclosed were not more than "well-understood, routine, conventional activity previously engaged in by researchers in the field. " *Mayo*, 132 S. Ct. at 1294. Likewise, in *Funk Bros* this Court concluded that "there is no invention here unless the discovery that certain strains of the several species of these bacteria are non-inhibitive and may thus be safely mixed is invention.

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[9] Claim 4 illustrates the claims of the patent-in-suit, U.S. Patent No. 2,200,532:

> 4. An inoculant for leguminous plants comprising a plurality of selected mutually non-inhibitive strains of different species of bacteria of the genus Rhizobium, said strains being unaffected by each other in respect to their ability to fix nitrogen in the leguminous plant for which they are specific.

Funk Brothers Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 128 n.1 (1948).

But we cannot so hold without allowing a patent to issue on one of the ancient secrets of nature now disclosed." *Funk Bros. Seed Co.,* 333 U.S. at132.

It was the properties of the strains (being non-inhibitory when certain strains were mixed together) that were the "ancient secret of nature now disclosed" and which formed the basis for the invention; mixing of the strains without that knowledge would be insufficient. *Id.* The Court considered mere mixing of the two strains insufficient to make claims to the co-cultures patentable.

Myriad's claims implicate none of the legal or policy concerns that arose in any of these prior cases, and nothing in these cases supports a determination that Myriad's claims to isolated human DNA are not eligible for patenting.

C. Isolated Human DNA as Claimed in the Patents-in-Suit is a Product of the "Hand of Man" and Hence is Patent-Eligible

Plaintiffs contend that claims of the patents-in-suit encompassing isolated human DNA encoding BRCA1 and BRCA2 are patent-ineligible based upon their status as being "products of nature." This contention is incorrect as a matter of law and as a matter of fact.

The claimed isolated human BCRA1 and BCRA2 DNA are not "products of nature" because, as claimed, they are not found in nature. These isolated human DNAs are never found "isolated" in nature. First, they are not merely associated with contaminants (like the "intracellular material" contaminating cellulose in the

Wood Paper Patent Cases); they are intrinsically (and covalently) attached to and are a part of the physical and chemical structure of the chromosomal DNA, and their isolation requires them to be separated from this DNA, *i.e.*, to be present in an entirely new chemical structure. As discussed above, in other (cDNA) embodiments the claimed isolated human DNA is also not merely "isolated" but chemically changed in the process, first by the cell in making mRNA, and again by the inventor in converting the mRNA into cDNA. Thus, the claimed subject matter is different, physically and chemically, from the DNA present in nature. They are also changed functionally, being capable *inter alia* for use as probes or for making recombinant proteins.

These differences are sufficient to distinguish the claimed isolated human DNA in the patents-in-suit from DNA as it occurs in nature. Prior decisions of this Court do not mandate a contrary result. In each of these prior cases, the Court was concerned with one (or both) of the following bars to patent-eligibility: that the claimed product was known in the art prior to the inventor's claim (actually, a bar to patentability), or that the claim was so broad that it encompassed a law or phenomenon of nature. Thus, in both the *Wood-Paper Patent Cases* and *Cochrane*, the claimed subject matter encompassed the prior art (cellulose and alizarine, respectively). In those cases, the products were known and used prior to the patent claim, and thus were unpatentable (rather than being patent-ineligible). And in the *Funk Brothers* case, the Court's concern was patenting the phenomenon of co-culture viability, particularly in view of the scope of the claims (*i.e.*, any combination of bacterial culture mixtures exhibiting the capacity to grow together without inhibition).

Neither situation exists in this case. DNA encoding BRCA1 and BRCA 2 was completely unknown prior to isolation and identification by the patentees. Indeed, the only thing that was known about these genes was that they *might* reside at a particular region of the human genome at each of two specific sites on human chromosomes[10] that were inherited by women who developed breast or ovarian cancer prematurely. What was known in the prior art was merely a phenotype, a predisposition to develop such cancers at a much higher rate than the average, and a correlation of the presence of the phenotype with these chromosomal sites. This was the "phenomenon of nature," the correlation, but while it provides value to these cloned isolated human DNAs, it is not *equivalent* to the genes themselves, which have their own chemical identities. Isolating these human DNAs is not equivalent to patenting the phenomenon, as in *Funk Brothers*, but as required by *Chakrabarty*, the isolated human DNAs are "nonnaturally occurring manufacture[s] or composition[s] of matter – . . . product[s] of human ingenuity [each] 'having a distinctive name, character [and] use.'" *Chakrabarty*, 447 U.S. at 309–10 (quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887)).

This conclusion would follow even if the proteins encoded by BRCA1 and BRCA2 had been known in the art, since the protein and the DNAs encoding them are chemically-distinct species; the fact that their sequences are related (by the genetic code) is not necessarily sufficient to put the skilled artisan in possession of the isolated human DNA merely by isolating the corresponding protein. *In re Kubin*, 561 F.3d 1351, 1361 (Fed. Cir. 2009). Here, the very existence of the protein encoded by each of the BRCA1 and BRCA2 genes was unknown.

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[10] On the long arm of chromosome 17 at position 21 (BRCA1) and on the long arm of chromosome 13 at position 12.3 (BRCA2).

The other line of reasoning, enunciated by the Court in *Funk Brothers* and recited with approval in *Chakrabarty* and more recently in *Mayo*, is that claims cannot encompass a "natural law" or "phenomenon of nature." Myriad's claims to isolated human DNA do neither. These claims recite man-made manufactures or compositions of matter, not phenomena. They are tangible, physical compounds, having particular and specific structures capable of being elucidated and described. They do not foreclose anything other than making, using, selling, offering to sell, or importing these specific and particular chemical compounds. As such, they are outside the limited range of subject matter proscribed from patent-eligibility by this Court's prior decisions and the Constitution's strictures, and are thus properly the subject of the patents-in-suit.

D. Patents to Isolated Human DNA do not Claim Genetic Information

Plaintiffs wrongly equate patenting of isolated human DNA with patenting genetic information. There is no dispute that genetic information, standing alone, is not patentable subject matter and does not belong to one of the statutory categories required for patent-eligibility. *See Chakrabarty*, 447 U.S. at 314. Indeed, information *per se*, like ideas, does not constitute patentable subject matter, *Rubber-Tip Pencil Co. v. Howard*, 87 U.S. 498, 507 (1874). Critically, however, patents on isolated human DNA do not claim or preempt genetic information. *See Bayer AG v. Housey Pharma., Inc.*, 340 F.3d 1367, 1377 (Fed. Cir.

2003) (holding "that in order for a produce to have been 'made by a process patented in the United States' [under 35 U.S.C. § 271(g)] it must have been a physical article that was 'manufactured' and that the production of information is not covered.") Patent claims to isolated DNA only cover the isolated DNA itself, and not the genetic information per se.

Indeed, plaintiffs' argument has it backwards. A great many of the known human genes were disclosed for the very first time in patent applications. This disclosure of genetic information was a beneficial byproduct of 35 U.S.C. § 112, which requires the disclosure of the invention "in such full, clear, concise, and exact terms" to permit one of ordinary skill in the art to make and use the invention. Thus, the patenting of isolated human DNA promotes progress in genetic research by requiring applicants to disclose what they know about the best mode of making and using isolated human DNA. This ability to patent isolated genes results in genetic information being freely available on public databases, both governmental (patent) and private, throughout the world.

The dichotomy between patent-eligible isolated human DNA and patent-ineligible genetic information is consistent with precedent. For example, in *O'Reilly v. Morse*, 56 U.S. 62, 63 (1853), the ability to use electricity for communication was found to be patent-ineligible, but the specific telegraph invented by Morse was determined to be patent-eligible. Algorithms *per se* have also been held to be patent-ineligible, *Parker v. Flook*, 437 U.S. 584, 585 (1978); *Gottschalk v. Benson*, 409 U.S. 63, 64 (1972), while the use of an algorithm (an equation) in a patented process has been found to be patent-eligible, *Diamond* *v. Diehr*, 450 U.S. 175, 177 (1981). These principles are consistent with the constitutional restrictions on the exercise of Congress' power to grant patents, *i.e.*, that they "promote the Progress of . . . useful Arts." U.S. Const. art. I, § 8, cl. 8.

II. A Ban on Patenting Isolated Human DNA Would Negatively Impact Research, Technology and Innovation, and be Contrary to the Constitutional Mandate That the Patent Act "Promote the Progress of . . . the Useful Arts"

Patents provide the incentive to invest the time, money, and manpower to understand what these genes encode and what the encoded proteins do, both being requirements imposed under 35 U.S.C. § 101 as interpreted by the U.S. Patent and Trademark Office. And once these characteristics and properties of genes and their encoded proteins are determined, they can be exploited for their various utilities, as they have for a generation in providing new and heretofore unavailable therapies. These include proteins like human Blood Clotting Factors VIII and IX, insulin, human growth hormone, erythropoietin, tissue plasminogen activator, and all monoclonal antibodies that are the basis for anticancer and other therapies. Any number of such drugs have been developed that, according to a recent Federal Trade Commission report, "have improved medical treatments, reduced suffering, and saved the lives of many Americans."[11] Biologics are predicted to become the most prescribed drugs over the next decade, to be used in the treatment of diseases such as cancer that have been otherwise incurable throughout human history. Today, such biologics include Enbrel® for treating rheumatoid arthritis; Rituxan® for non-Hodgkin's lymphoma; Remicade® for Crohn's disease, arthritic, ulcerative colitis, and other inflammatory disorders; and Avastin® for colon cancer. In 2008, biologics comprised 39% of drug revenues.[12] Biologic drug products are expected to account for 75% of drug revenues by 2014, and additionally to include Herceptin® for breast cancer, Lantus® for diabetes, and Humira® for arthritis. Biologics thus treat chronic diseases of aging and are particularly important for the U.S. public as well as the U.S. economy.

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[11] FEDERAL TRADE COMMISSION REPORT, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION, i (2009), *available at* http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf.

Biologics, like other drugs, are cost-and investment-intensive to develop and commercialize, and may in fact be more expensive than conventional therapeutic drugs. Development of a single biologic drug product can take up to 12 years and cost over $1 billion to bring to market.[13] Even the manufacturing facilities required to make biologics are more expensive to build than conventional drug manufacturing plants, costing between $400 and $500 million.[14] Patent protection is necessary to support this level of investment, and its absence can be expected to severely inhibit further development of biologic drugs.[15] Patents on isolated human DNA protect the means for making many of these biologic drugs and their absence due to a ban would negatively impact the ability of such drugs to be developed.

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[12] Biosimilars 101, Credit Suisse, 6 (2009), *available at* http://www.scribd.com/doc/53368888/20090824-Biosimilar-theme-report.

[13] JIM HOLLINGSHEAD & ROB JACOBY, AVOIDING NO MAN'S LAND: POTENTIAL UNINTENDED CONSEQUENCES OF FOLLOW-ON BIOLOGICS 9 (2009), *available at* http://www.pharmamanufacturing.com/Media/1001/Deloitte_Biosimilars.pdf.

[14] *Squawkbox* (CNBC television broadcast Aug. 9, 2009) (comments of James Greenwood, President of the Biotechnology Industry Organization BIO), *available at* http://www.cnbc.com/id/15840232?video=1213899782&play=1.

A. Genetic Information is the Basis for the Coming Era of Personalized Medicine and Requires Patents to Promote Investment and Development

One of the most promising benefits of the elucidation of human genetic sequence information is the development of personalized medicine, the use of genetic information for diagnosing disease propensity and making improved therapeutic choices.[16] Examples of how this technology can be used include pharmacogenomics, defined as "the application of genomic and molecular data to better target the delivery of health care, facilitate the discovery and clinical testing of new products, and help determine a person's predisposition to a particular disease or condition."[17] Currently, the technology includes detection of enzyme variants for identifying patients susceptible to adverse reactions to the anticoagulant drug coumarin,[18] and identifying molecular markers for making cancer treatment decisions.[19]

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[15] Amicus brief on behalf of the Biotechnology Industry Organization, *Bilski v. Kappos*, No. 08-964 (Aug. 6, 2009).

[16] Anil Potti et al., *A Genomic Strategy to Refine Prognosis in Early-Stage Non-Small-Cell Lung Cancer*, 355 NEW ENG. J. MED.. 570, 578–79 (2006); Wolfgang Sadee & Zunyan Dai, *Pharmacogenetics/Genomics and Personalized Medicine*, 14 HUMAN. MOL. GENET. R207, R207 (2005).

[17] Genomics and Personalized Medicine Act of 2007, S. 976, 11th Cong. § 2 (2007), *available at* www.govtrack.us/congress/bill.xpd?bill=s110-976 ("A bill [t]o secure the promise of personalized medicine for all Americans by expanding and accelerating genomics research and initiatives to improve the accuracy of disease diagnosis, increase the safety of drugs, and identify novel treatments.").

Development of personalized medicine is thus important for diagnosing diseases, the propensity for developing diseases (including chronic diseases like cancer and diabetes), and making informed and effective treatment decisions. Indeed, researchers have developed a "gene chip"[20] that can be interrogated to detect hundreds of mutations in up to 170 genes relating to drug metabolism.[21] Continued development of this technology will depend on patent protection to provide the incentive for investment.

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[18] U. I. Schwarz, *Clinical Relevance of Genetic Polymorphisms in the Human CYP2C9 Gene*, 33 Eur. J. Clin. Invest., 23, 33 (2003).

[19] John C. Mansour & Roderich E. Schwarz, *Molecular Mechanisms for Individualized Cancer Care,* 207 J. Am. Coll. Surg. 250 (2008); Laura J. van't Veer & René Bernards, *Enabling Personalized Cancer Medicine Through Analysis of Gene-Expression Patterns*, 452 Nature 564 (2008).

[20] A gene chip, or microarray, is described *inter alia* in DNA Microarrays: A practical approach, (Mark Schena, ed., 1999).

[21] *Personalized Medicine Advancing*, UPI.com (Dec. 31, 2009, 2:10 PM), www.upi.com/Health_News/2009/12/31/Personalized-medicine-advancing/UPI-44821262286609/.

B. A Ban on Patenting Isolated Human DNA Would Promote Suppression of Genetic Information Relevant to Diagnostic and Therapeutic Applications

Banning patents on isolated human DNA and patents on diagnostic uses of genetic information will provide incentives for this technology to be developed in a way that can be protected. And in the absence of patenting, this will most likely involve trade secret protection.

The isolated human DNA and diagnostic methods claimed in the patents-in-suit represent a rare and possibly unique genetic situation: mutations in one or two genes that increase a woman's propensity to develop breast or ovarian cancer from 5-10% to 95% (recalling that estimates of breast cancer in the general population are about 1 in 8 (12.5%)[22] and, for ovarian cancer, 1 in 100 (1.0%)[23]). While similar "propensity for disease" genes have been identified,[24] most diseases are different: they are the result of several inherited and/or acquired changes in gene structure, expression, or function. Thus, it will be more difficult to determine genetic changes and patterns thereof that reliably indicate an increased likelihood of developing diseases like diabetes,[25] cardiovascular disease,[26] autism,[27] Parkinson's disease,[28] Alzheimer's disease,[29] immunological disorders,[30] asthma[31], and most forms of cancer.[32] A critical review of the field concluded that "[g]enetic profiling may have the potential to identify individuals at higher risk of disease depending on the prevalence and heritability of the disease"[33] and a separate study on prostate cancer found that "[t]he genetic basis of many common human diseases is expected to be highly heterogeneous, with multiple causative loci and multiple alleles at some of the causative [genetic] loci."[34]

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[22] *Breast Cancer Statistics & Survival Rates*, IMAGINIS.COM, www.imaginis.com/breasthealth/statistics.asp (last visited Jan. 14, 2010).

[23] *Hereditary Breast and Ovarian Cancer*, CDC, *http://www.cdc.gov/features/hereditarycancer/ (last updated Oct. 18, 2010).*

[24] An example is familial adenomatous polyposis. *See Familial Adenomatous Polyposis*, GENETIC HOME REFERENCE (2008),ghr.nlm.nih.gov/condition=familialadenomatouspolyposis.

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[25] Saxena et al., *Genome-Wide Association Analysis Identifies Loci for Type 2 Diabetes and Triglyceride Levels*, 316 SCIENCE 1331 (2007).

[26] Matthew Kelly & Christopher Semsarian, *Multiple Mutations in Genetic Cardiovascular Disease: A Marker of Disease Severity?*, 2 CIRCULATION CARDIOVASCULAR GENETICS 182, 182 (2009).

[27] Deborah Halber, *Multiple Genes Implicated in Autism; Discovery Could Lead to Drugs Targeting Gene Interactions*, SCIENCEDAILY (Feb. 10, 2009), www.sciencedaily.com/releases/2009/02/090209205049.htm.

[28] William K. Scott et al., *Complete Genomic Screen in Parkinson Disease: Evidence for Multiple Genes*, 286 J. AM. MED. ASSOC. 2239, 2239 (2001).

[29] Nienwen Chow et al., *Expression Profiles of Multiple Genes in Single Neurons of Alzheimer's Disease*, 95 PROCEEDINGS OF THE NAT. ACAD. OF SCI. USA 9620, 9620 (1998).

[30] Vesela Gateva et al., *A Large-Scale Replication Study Identifies TNIP1, JAZF1, UHRF1BP1 and IL10 as Risk Loci for Systemic Lupus Erythematosus*, 41 NATURE GENETICS 1228, 1229 (2009).

[31] Kate G. Ackerman et al., *Interacting Genetic Loci Cause Airway Hyperresponsiveness*, 21 PHYSIOL. GENOMICS 105, 105 (2005).

[32] Wei Jiang et al., *Constructing Disease-Specific Gene Networks Using Pair-Wise Relevance Metric: Application to Colon Cancer Identifies Interleukin 8, Desmin and Enolase 1 as Central Elements*, 2 BMC SYS. BIO. 72, 73 (2008).

As a consequence, it can be expected that most human diseases will be multigenic in origin and vary with race, ethnicity, age, and other variables.[35] The studies cited herein are but the beginnings of this technology. Absent patent protection, and under the circumstances of multigenic causation (or at least association) of common diseases, the impetus will be to develop and protect this nascent technology using, *inter alia*, trade secret protection.

Such tests could be developed as follows. A gene chip (as discussed above) could be developed to contain isolated human DNA that is diagnostic for a disease (such as prostate cancer) in a defined population (such as African American men). Multiple genes whose expression or sequence suffers genetic alteration in prostate cancer could be identified from archival normal and prostate cancer tissue samples that are available in multiple cancer tissue banks, both public and private. Isolated human DNAs specific for these genes, or alternations or mutations in these genes, could be included in a gene chip containing thousands of unrelated DNAs; indeed, each chip could contain several iterations of isolated human DNAs from the diagnostic genes, at both diagnostic (*i.e.*, mutated) and control (*i.e.*, "normal") sites. Disease or propensity for disease would be determined by identifying diagnostic isolated human DNAs contained on the chip for the genes of interest.

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[33] A. Cecile J. W. Janssens et al., *Predictive Testing for Complex Diseases Using Multiple Genes: Fact or Fiction?*,8 GENETICS IN MED. 395, 395 (2006).

[34] Daniel J. Schaid et al., *Nonparametric Tests of Association of Multiple Genes with Human Disease,* 76 AM. J. HUMAN GENETICS 780, 780 (2005).

[35] Stephen B. Liggett et al., *A GRK5 Polymorphism That Inhibits β-Adrenergic Receptor Signaling is Protective in Heart Failure,* 14 NAT MED. 510, 511 (2008).

The development of bioinformatics[36] methods makes possible production of a plurality of such chips containing several (up to hundreds) of isolated human DNAs that are diagnostic for the disease of interest, and positive and negative control isolated human DNAs that will be detected *vel non* in all (or almost all) samples. In addition, such chips could contain thousands of unrelated isolated human DNAs. The technology could permit each chip to be encoded in such a way (with a bar code, for example) that would uniquely identify for each chip a pattern indicative of disease presence or propensity. In the absence of patent protection, such information could be kept proprietary, *i.e.*, only the company providing the test would have knowledge of the genes involved in the test or the diagnostic pattern of detected alterations in particular genes or their expression. The encypted bar code could relate each chip uniquely with a pattern that indicated disease, disease propensity or the absence of either. Such information could be kept as a trade secret because the large number of isolated human DNAs on each chip would be sufficient to effectively preclude reverse engineering of the chips to determine which collections of genes and which alternations in sequence or expression are diagnostic. Under these circumstances, innovation in genetic-based diagnostics would be severely limited, since there would be no incentive (indeed, there would be strong *dis*incentives) to disclose the genetic basis of the diagnostic assay. This information, as a trade secret, could be kept out of the public domain indefinitely.

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[36] A term used to describe the application of computer analysis to genetic sequences. *See*: *Bioinformatics*, WIKIPEDIA, http://en.wikipedia.org/wiki/Bioinformatics (last modified March 1, 2013).

C. Patenting Isolated Human DNA does not Impede Basic Research

Patenting isolated human DNA does not impede, or indeed impact to any significant degree, basic genetic research, a conclusion supported by an overwhelming majority of analyses reported over the past ten years on the effects of such patents, from the U.S.,[37] Germany,[38]

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[37] John P. Walsh, Charlene Cho & Wesley M. Cohen, *Science and Law: View from the Bench: Patents and Material Transfers*, 309 SCIENCE 2002, 2002 (2005); John P. Walsh, Ashish Arora & Wesley M. Choehen , *Science and the Law: Working Through the Patent Problem*, 299 SCIENCE 1021, 1021 (2003).

[38] ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT, GENETIC INVENTIONS, INTELLECTUAL PROPERTY RIGHTS AND LICENSING PRACTICES 47 (2002), *available at* http://www.oecd.org/dataoecd/42/21/2491084.pdf.

Australia,[39] and Japan.[40] A specific (predicted) consequence of patenting isolated human DNA, the creation of patent "thickets" that would impede research (provocatively termed the "tragedy of the anticommons[41]), has had no substantive effect on basic academic research,[42] even when researchers focused their inquiry on precisely those research reports relating to practical applications of biotechnology.[43] Indeed, it was reported (in a study done by the American Association for the Advancement of Science on the effects of patenting isolated human DNA on basic research in the U.S., Europe (Germany and the U.K), and Japan) that "all four studies suggest that intellectual property rights had little negative impact on the practice of science."[44] More recently, a study from the Catholic University in Leuven, Belgium showed that legal uncertainty, not patents on isolated human DNA, caused the principal negative effect on genetic diagnostic testing.[45]

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[39] DIANNE NICOL & JANE NIELSEN, PATENTS AND MEDICAL BIOTECHNOLOGY: AN EMPIRICAL ANALYSIS OF ISSUES FACING THE AUSTRALIAN INDUSTRY, CENTRE FOR LAW & GENETICS, OCCASIONAL PAPER 6 (2003), *available at* http://www.ipria.org/publications/reports/BiotechReportFinal.pdf.

[40] Sadao Nagaoka, An Empirical Analysis of Patenting and Licensing Practice of Research Tools from Three Perspectives, presented in OECD Conference in Research Use of Patented Inventions, 22 (May 2006), *available at* http://www.oepm.es/cs/OEPMSite/contenidos/ponen/conferenciantes/archivosPDF/36816178.pdf.

[41] Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698, 699 (1998).

[42] *See* Carl Shapiro, *Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Standard Setting*, *in* 1 INNOVATION POLICY AND THE ECONOMY 119, 120 (Adam B. Jaffe, Josh Lerner and Scott Stern eds., 2001); John Walsh, Ashish Arora & Wesley M. Cohen, *Effects of Research Tool Patenting and Licensing and Biomedical Innovation*, *in* PATENTS IN THE KNOWLEDGE-BASED ECONOMY 285 (Wesley M. Cohen and Stephen A. Merrill, eds. 2003); Zhen Lei, Rakhi Juneja & Brian D. Wright, *Patents Versus Patenting: Implications of Intellectual Property Protection for Biological Research*, 27 NAT. BIOTECH. 36, 36 (2009); Ronald Bailey, *The Tragedy of the Anticommons: Do Patents Actually Impede Innovation?*, REASON.COM (Oct. 2, 2007), www.reason.com/archives/2007/10/02/the-tragedy-of-the-anticommons.

The results of these studies are consistent with the experience of the scientific community on the effects of the BRCA1 and BRCA2 patents on research activity on these genes. Perhaps the best measure of such activity is the number of research reports in public databases that reflect ongoing basic scientific research in peer-reviewed scientific journals. While reported estimates differ depending on the search term used, a simple search of "brca1 or brca2" resulted in 10,652 publications, the most recent of which was published on February 20, 2013.[46] U.S. Patent No. 5,747,282, directed to isolated human DNA encoding BRCA1, issued on May 5, 1998, and U.S. Patent No. 5,837,492, directed to isolated human DNA encoding BRCA2, issued on November 17, 1998. If either of these patents had a chilling effect on basic research, the expectation would be that the number of scientific research reports would have declined in the face of these patents. On the contrary, the number of such publications has steadily increased each year, which is precisely what would be expected if these patents had no significant effect on basic scientific research.

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[43] Fiona Murray & Scott Stern, *Do Formal Intellectual Property Rights Hinder the Free Flow of Scientific Knowledge? An Empirical Test of the Anti-commons Hypothesis*, 63 J. ECON. BEHAVI. & ORG. 648 (2007).

[44] Beck Ham, *Research Not Slowed by Intellectual Property Protections, AAAS Surveys Find*, AAAS.ORG (May 28, 2007), http://www.aaas.org/news/releases/2007/0529sippi.shtml. *See* AAAS, INTERNATIONAL INTELLECTUAL PROPERTY EXPERIENCES: A REPORT of FOUR COUNTRIES, 14–15 (Hansen, ed., 2007).

[45] Isabelle Huys et al., *Legal Uncertainty in the Area of Genetic Diagnostic Testing*, 27 NAT. BIOTECH. 903 (2009).

What these patents do, of course, is prevent commercial activity – using the patented isolated human DNA or performing the patented methods for profit. This is a legitimate exercise of the patent grant.

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[46] L. Bonanno et al., *The Predictive Value of BRCA1 and RAP80 mRNA Expression in Advanced Non-Small-Cell lung Cancer Patients Treated with Platinum-Based Chemotherapy*, ANN. ONCOL (February 20, 2013) (Epub ahead of print).

CONCLUSION

For all the reasons set forth herein, *amicus curiae* IPO asks the Court to affirm the Federal Circuit's decision that claims to isolated human DNA are patent-eligible.

Respectfully submitted,

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AMICUS CURIAE BRIEF

Supreme Court, U.S.
FILED

JAN 3 1 2013

OFFICE OF THE CLERK

No. 12-398

IN THE
Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY,
ET AL.,

Petitioners,

v.

MYRIAD GENETICS, INC., ET AL.,

Respondents.

ON WRIT OF CERTIORARI
TO THE UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

BRIEF FOR *AMICI CURIAE* INTERNATIONAL CENTER FOR TECHNOLOGY ASSESSMENT, COUNCIL FOR RESPONSIBLE GENETICS, GREENPEACE, INDIGENOUS PEOPLES COUNCIL ON BIOCOLONIALISM, FRIENDS OF THE EARTH, AND CENTER FOR ENVIRONMENTAL HEALTH IN SUPPORT OF PETITIONERS

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U.S. Patent No. 5,397,696 (issued Mar. 14, 1995) 26

INTERESTS OF *AMICI CURIAE*[1]

Amici are public interest, non-profit organizations that oppose the patenting of genes because genes are products of nature. *Amici* seek to provide the Court with insight into the broader adverse effects of gene patents such as Respondent Myriad Genetics' Breast Cancer Susceptibility Genes 1 and 2 (collectively BRCA or BRCA1-2). These areas are central to *Amici*'s organizational missions and work, including gene patents' scientific, cultural, indigenous, and environmental impacts. These significant impacts can and should be avoided, because genes are not patentable subject matter.

Amicus **International Center for Technology Assessment (ICTA)** is a non-profit organization devoted to analyzing the economic, environmental, ethical, political, and social impacts that can result from the application of new technologies or technological systems. ICTA is jointly affiliated with the non-profits Center for Food Safety and Foundation Earth. ICTA's *PatentWatch* Project works to expose and challenge the inappropriate use of the U.S. patent system.

Amicus **Council for Responsible Genetics (CRG)** is a national non-profit organization dedicated to representing the public interest and fostering public debate about the social, ethical, and environmental implications of genetic technologies. CRG's *Genetic Bill of Rights* outlines the fundamental values that have been put at risk by new applications of genetics and specifically opposes gene patents. CRG publishes *GeneWatch*, a periodical that regularly includes articles by experts in the field on issues related to gene patents.

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[1] Petitioners have lodged a blanket consent to the filing of *amicus* briefs, and a letter of consent to the filing of this brief by Respondents has been lodged with the Clerk of the Court. No counsel for any party in this case authored this brief in whole or in part, and no person or entity other than *Amici Curiae* made a monetary contribution to its preparation or submission.

Amicus **Greenpeace, Inc**. is the leading independent campaigning organization that uses peaceful direct action and creative communication to expose global environmental problems and to promote solutions that are essential to a green and peaceful future. Greenpeace's report, *The True Cost of Gene Patents*, details the severe economic and social consequences of patenting genes and living organisms.[2]

Amicus **Indigenous Peoples Council on Biocolonialism (IPCB)** is a non-profit Indigenous peoples' organization that seeks to protect the Indigenous knowledge, cultural heritage, and genetic materials of Indigenous peoples. IPCB monitors and evaluates the complex linkages between biotechnology, intellectual property rights, and the forces of globalization in relation to Indigenous peoples' rights and concerns.

Amicus **Friends of the Earth (FoE)** is a non-profit organization founded in 1969 and its mission is to defend the environment and champion a healthy and just world. FoE's campaigns focus on promoting clean energy and solutions to climate change, keeping toxic and risky technologies out of the food we eat and products we use, and protecting marine ecosystems and the people who live and work near them.

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[2] Greenpeace, Inc., *The True Cost of Gene Patents*, June 15, 2004, *available at* http://www.greenpeace.org/international/en/publications/reports/the-true-cost-of-gene-patents/ (last visited Jan. 29, 2013).

Amicus **Center for Environmental Health (CEH)** is a non-profit organization dedicated to protecting the public from environmental and public health hazards. CEH is committed to environmental justice, promoting a safe and sustainable food supply, supporting communities in their quest for a safer environment, and fostering corporate accountability.

SUMMARY OF ARGUMENT

Respondent Myriad Genetics' patents are contrary to one hundred and fifty years of precedent in which this Court has held that the products and laws of nature are not patentable subject matter. Gene sequences, DNA, and cDNA are products of nature. Genes also embody laws of nature, because they are quintessentially information, in the form of DNA. Myriad did not invent the patented DNA, nor its useful characteristics or functions. Myriad's extraction of the patented genes from the body (isolation) does not alter that conclusion.

Petitioners and several other *Amici* comprehensively detail how gene patents impede crucial research and interfere with medical care, to the detriment of patients, doctors, non-profit organizations, and researchers. Yet, as serious as these harms are, there are unfortunately further significant scientific, cultural, and environmental impacts flowing from these patents.

First, privatizing genes creates rights of unknown scope and significance, because science currently lacks a holistic understanding of their roles vis-à-vis non-hereditary proteins, other DNA sequences that are not genes, RNA, the cellular environment, and the extra-human environment. Recent scientific research fatally belies prior assumptions of the gene as the *sine qua non* of biology and heredity, and instead reveals a more complex and nuanced relationship and role of DNA in the body. The patenting of one biological "building block" in this epigenetic dynamic hampers scientific advancement, a result that is antithetical to the basic purpose of patent law.

Second, because genes are fundamentally encoded storehouses of information, gene patents deny the public access to natural genetic data, in contravention of the public good. These patents violate fundamental common law precepts of common heritage, the public domain, and the public trust.

Finally, gene patents privatize genetic ancestry, making Indigenous peoples and medical patients into "treasure troves" to be exploited for economic gain, in violation of cultural and religious values, and basic rights to informed consent.

For these reasons, *Amici* request the Court reverse the Federal Circuit and hold the patent claims invalid.

ARGUMENT

I. GENES ARE NOT PATENTABLE SUBJECT MATTER

For more than a century and a half, this Court has held that the laws and phenomena of nature are not patentable, as required by Article I, Section 8, Clause 8 of the U.S. Constitution (the patent clause of the U.S. Constitution), as well as 35 U.S.C. § 101 (the patent statute subject matter requirements). *See, e.g.*, *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980); *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948); *Am. Wood-Paper Co. v. Fibre Disintegrating Co.*, 90 U.S. 566, 593-94 (1874); *see also J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 130, 134 (2001); *Diamond v. Diehr*, 450 U.S. 175, 185 (1981); *Parker v. Flook*, 437 U.S. 584, 593 (1978); *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972); *O'Reilly v. Morse*, 56 U.S. (15 How.) 62, 112-121 (1854); *Le Roy v. Tatham*, 55 U.S. (14 How.) 156, 175 (1853). The Court has recently twice reaffirmed this doctrine. *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1293-94 (2012); *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010).

Natural laws and phenomena are "nature's handiwork," *Chakrabarty*, 447 U.S. at 310, "the basic tools of scientific and technological work," *Gottschalk*, 409 U.S. at 67. As such, the doctrine establishes a "bright-line prohibition against patenting laws of nature" which also serves as a "proxy for the underlying 'building block' concern." *Mayo*, 132 S. Ct. at 1303. Hence "patents cannot issue for the discovery of the phenomena of nature," which are "part of the storehouse of knowledge of all men. They are manifestations of laws of nature, free to all men and reserved exclusively to none." *Funk Bros.*, 333 U.S. at 130 (citing *Le Roy*, 55 U.S. (14 How.) at 175); *accord Bilski*, 130 S. Ct. at 3225; *Chakrabarty*, 447 U.S. at 309.

Permitting the patenting of these indispensable building blocks is contrary to the fundamental purposes of patent law, because it would "monopoliz[e]" those "basic tools of scientific and technological work," "impede innovation more than . . . promote it," *Mayo*, 132 S. Ct. at 1293, and "risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in making further discoveries," *id.* at 1294.

Applying the doctrine to the question presented, the answer is plain: genes, specifically here Myriad's patented BRCA genes, are not patentable. There is no "invention" here. *Chakrabarty*, 447 U.S. at 309. In contrast to "products of nature," "human-made inventions" based upon them are to be "markedly different." *Id.* at 310, 313. The patented genes are a far cry from being "markedly different" than what occurs in nature; they are identical. If a "new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter," than neither is a new gene discovered in the body. *Mayo*, 132 S. Ct. at 1293 (quoting *Chakrabarty*, 447 U.S. at 309).

A substance whose characteristics and function are indistinguishable from those of its naturally-occurring counterpart cannot constitute patentable subject matter. *Funk Bros.*, 333 U.S. at 130-31. In

Funk Brothers, the Court held that certain root nodule bacteria mixtures used to inoculate plant seeds were not patentable because "[e]ach species has the same effect it always had . . . Their use in combination does not improve in any way their natural functioning. They serve the ends nature originally provided and act quite independently of any effort of the patentee." *Id.* at 131 (emphases added).[3] The same is true here: the structure and function of genes are created by nature. The patented gene sequences here serve the ends nature originally provided and act independently of any effort of Respondents.

Nor does the fact Respondents "isolated" the genes matter. Isolation is a not an "inventive concept." *Mayo*, 132 S. Ct. at 1294, 1297; *see also Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1302 (Fed. Cir. 2007) ("[I]solation of interesting compounds . . . 'is likely the product not of innovation but of ordinary skill and common sense.'") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)). The mere removal of a product of nature from its natural environment is insufficient to confer inventive status. *Am. Wood-Paper Co.*, 90 U.S. at 593-94 ("A process to [extract something] from a subject from which it has never been taken may be the creature of invention, but the thing itself when obtained cannot be called a new manufacture."). Diverting (also known as "isolating") water from a river, or plucking (also known as "isolating") a leaf from a tree or a feather from a bird, do not make those substances patentable. *See, e.g.*, *Ex parte Latimer*, 1889 Dec. Comm'r Pat. 123, 125-126 (1889) (rejecting claim for "purified pine needle fiber"); *Gen. Elec. Co. v. DeForest Radio Co.*, 28 F.2d 641, 643 (3d Cir. 1928) (rejecting claim for "pure tungsten"), *cert. denied* 278 U.S. 656 (1929); *In re Marden*, 47 F.2d 958, 959 (C.C.P.A. 1931) (rejecting claim for "pure vanadium"). The gene, once isolated, is not subsequently "markedly different" in either structure or function. *Chakrabarty*, 447 U.S. at 310.

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[3] *See also Am. Wood Paper Co.*, 90 U.S. at 593-94 (cellulose derived from wood pulp by a new process not patentable because it was indistinguishable from cellulose previously obtained from other sources via existing processes); *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 311 (1884) (holding artificial alizarine (a dye) derived from a new process unpatentable because the claimed product was indistinguishable from that obtained naturally).

The patented substances are also not eligible subject matter because genes, as the carriers of DNA, are the physical embodiment of laws of nature. *See Funk Bros.*, 333 U.S. at 130 (products of nature are "manifestations of laws of nature, free to all men and reserved exclusively to none"). Gene sequences are not the same as conventional chemical substances. Rather, they are fundamentally information—an informational molecule embodying the genetic code. The patented genetic sequences' importance stems from their ability to encode and transmit this information, as instructions to the body. As such, this natural-law–natural-phenomena relationship is analogous to the *Mayo* Court's teaching that the prohibition on patenting laws of nature is a "proxy" for the "underlying building block." 132 S. Ct. at 1303 (quotations omitted).

Here, the information transmitted by the gene is identical, whether inside or outside the body. The useful properties of a gene are not ones that a scientist has invented (or created through isolation), but rather are the natural, inherent properties of genes themselves. *Funk Bros.*, 333 U.S. at 130-31. Mere "isolation" of natural phenomena, particularly ones that are the literal "manifestation" of natural laws, cannot create patentable subject matter. As in *Mayo*, "simply appending conventional steps" to "laws of nature" or "natural phenomena" "cannot make those laws, phenomena, and ideas patentable." 132 S. Ct. at 1300; *accord Parker*, 437 U.S. at 590.[4]

II. GENE PATENTS ARE PROPERLY EXCLUDED FROM PATENTABLE SUBJECT MATTER BECAUSE THEY HAVE SIGNIFICANT NEGATIVE SCIENTIFIC, SOCIAL, CULTURAL, AND ENVIRONMENTAL CONSEQUENCES

In *Mayo*, this Court reiterated why it is essential not to have patents on products of nature or laws of nature:

> "Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the

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[4] The Court need not reach the issue of cDNA, since Myriad's patents extend far beyond it; however if it does, the analysis is the same. cDNA's structure and function is created by nature, and it is not different when isolated. *Ass'n for Molecular Pathology v. USPTO*, 702 F. Supp. 2d 181, 198 (S.D.N.Y. 2010) ("[N]aturally occurring cDNAs, known as 'psuedogenes,' exist in the human genome and are structurally, functionally, and chemically identical to cDNAs made in the laboratory."). Permitting the patenting of cDNA would have the same negative impact of preempting basic scientific building blocks, and hampering future scientific progress.

> basic tools of scientific and technological work." And monopolization of those tools through the grant of a patent might tend to impede innovation more than it would tend to promote it.

132 S. Ct. at 1293 (quoting *Gottschalk*, 409 U.S. at 67); *see also Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 126-27 (2006) (Breyer, J., dissenting), *dismissing cert. granted to* 370 F.3d 1354 (Fed. Cir. 2004) ("Rather, the reason for the exclusion is that sometimes too much patent protection can impede rather than 'promote the Progress of Science and useful Arts,' the constitutional objective of patent and copyright protection.") (emphasis in original) (quoting U.S. Const. art. I, § 8, cl. 8).

Recent scientific advances have undermined prior assumptions of the gene's role, and instead revealed a much more complicated and nuanced relationship between the DNA and the human body. Privatizing these building blocks of a larger systemic and not-yet-understood field further impedes the progress of science. The privatization of genetic heritage also violates fundamental common law precepts of common heritage, the public domain, and the public trust. Finally, the granting of gene patents creates a system where people are reduced to "treasure troves" to be mined for private economic gain, violating the fundamental rights of indigenous peoples as well as patients.

A. Gene Patents Privatize Genetic Information of Which Scientists Lack a Full Understanding, Creating Rights of Unknown Scope and Significance, and Consequently Retarding, Rather than Furthering, the Progress of Science.

Gene sequences are not akin to a conventional chemical substance or a drug; they are instead fundamentally information, an informational molecule embodying the genetic code. The patent for a particular gene sequence patents the information contained in the sequence—for example, the As, Ts, Cs, and Gs of the genetic code. *See, e.g.*, Sunny Bains, *Double Helix Doubles as Engineer*, 279 Sci. 2043, 2043-44 (1998) (detailing the four bases making up DNA: cytosine, guanine, adenine, and thymine). The tens of thousands of genes in our bodies are involved in the production of over one-hundred thousand biological proteins. *See, e.g.*, Alan E. Guttmacher & Francis S. Collins, *Genomic Medicine—A Primer*, 347 New Eng. J. Med. 1512, 1514 (2002). The patent holder that purports to describe one commercial use should not then have a monopoly on all possible functions, particularly given that each commercial use covers only a small amount of what the patented gene does. *Funk Bros.*, 333 U.S. at 132 ("[W]e cannot so hold without allowing a patent to issue on one of the ancient secrets of nature now disclosed.").

More fundamentally, genes are substances that we still know little about, and about which scientific views have recently evolved significantly. *See, e.g.*, Carl Zimmer, *Now: The Rest of the Genome*, N.Y. Times, Nov. 11, 2008, at D1 (discussing the current gene "identity crisis" and how "new large-scale studies of DNA are causing [scientists] to rethink the very nature of genes"); Christopher Chabris et al., *Most Reported Genetic Associations with General Intelligence Are Probably False Positives*, 23 Psychol. Sci. 1314, 1314-23 (2012); Brendan Maher, *Personal Genomes: The Case of the Missing Hereditability*, 456 Nature 18, 18-21 (2008). Our evolving knowledge of human genes makes it imperative that such fundamental building blocks remain in the public domain.

For example, it was long believed that, because of the complexity of the human organism, people would have significantly more genes than other life forms, with estimates between one and two hundred thousand genes. The surprising results of the 2001 Human Genome Project show that humans actually have only about twenty thousand genes, a similar count to worms, flies, and yeast. *See, e.g.*, Elizabeth Pennisi, *Working the (Gene Count) Numbers: Finally, a Firm Answer?*, 316 Sci. 1113 (2007); *The Human Microbiome: Me, Myself, Us*, Economist, Aug. 18, 2012 (noting that humans have twenty-three thousand genes, dwarfed by the three million bacteria genes in each individual).

Instead, we now know that very minor changes in an individual's DNA sequences (not just the sequences that make proteins) can cause significant differences between even individual humans. Gina Kolata, *Study Discovers Road Map of DNA; A Key to Biology*, N.Y. Times, Sept. 6, 2012, at A1 ("As scientists delved into the 'junk'—parts of the DNA that are not actual genes containing instructions for proteins—they discovered a complex system that controls genes."); *id.* ("The human genome is packed with at least four million gene switches that reside in bits of DNA that once were dismissed as 'junk' but that turn out to play critical roles in controlling how cells, organs and other tissues behave. The discovery, considered a major medical and scientific breakthrough, has enormous implications for human health because many complex diseases appear to be caused by tiny changes in hundreds of gene switches."). As researchers discover more about these other human DNA components, the danger of gene patents halting further research and discovery is obvious. *Mayo*, 132 S. Ct. at 1294 (warning against the "danger" of claims "so abstract and sweeping as to cover both known and unknown uses" of the subject matter such that their use will "inhibit future innovation") (citing *Gottschalk*, 409 U.S. at 67-68); *O'Reilly*, 56 U.S. (15 How.) at 113 ("For aught that we now know some future inventor, in the onward march of science, may discover a mode of writing or printing . . . without using any part of the process or combination set forth in the plaintiff's specification . . . . But yet if it is covered by this patent the inventor could not use it, nor the public have the benefit of it.").

Hence, current research indicates that human complexity does not come primarily from genes, but instead must be related to other elements of our biology and the outer environment including: 1) the non-coding elements of DNA, so-called "junk" DNA accounting for more than 98% of all DNA, which is now seen to play a far more important role in regulating gene function than previously thought; 2) a cell's RNA often believed to be merely a "messenger" for genes, now understood to play a more important part in heredity and the causation of hereditary disease; and 3) the identity and number of the many hundreds of thousands of proteins in a cell, which often have a controlling influence on the action of genes—these proteins are viewed as critical biological actors in heredity and incidence of cancer and other disease. The ENCODE Project Consortium, *Identification and Analysis of Functional Elements in 1% of the Human Genome by the ENCODE Pilot Project*, 447 Nature 799, 799-816 (2007); Kolata, *supra*, at A1 (discussing the 2012 publication of several dozen groundbreaking scientific articles on the ENCODE findings); *id.* ("Most of the changes that affect disease don't lie in the genes themselves; they lie in the switches.") (quoting Professor Michael Snyder of Stanford University); *see also* Rick Weiss, *Intricate Toiling Found in Nooks of DNA Once Believed to Stand Idle*, Wash. Post, June 14, 2007 (reporting "[t]he first concerted effort to understand all the inner workings of the DNA molecule is overturning a host of long-held assumptions about the nature of genes and their role in human health"); Elizabeth Pennisi, *Genomics: DNA Study Forces Rethink of What It Means to Be a Gene*, 316 Sci. 1556, 1556-57 (2007) (stating that the research reveals an extremely different picture of DNA, RNA, protein, and their interactions than the one that scientists have assumed for decades).

Environmental influences can also affect DNA. Oliver Burkeman, *Why Everything You've Been Told About Evolution Is Wrong*, Guardian, Mar. 18, 2010, at G2-6 ("Rather than genes simply 'offering up' a random smorgasbord of traits in each new generation, . . . it seems that the environment plays a role in creating those traits in future generations."). New findings in the field of epigenetics show that environmental factors such as diet, stress, and prenatal nutrition can change genetic activity across at least one successive generation, even where genetic code may not be altered. John Cloud, *Why Your DNA Isn't Your Destiny*, Time, Jan. 6, 2010; *see also* Kara Rogers, *Epigenetics: A Turning Point in Our Understanding of Heredity*, Sci. Am., Jan. 16, 2012 ("This type of finding—an inherited difference that cannot be explained by variations in genes themselves—has become increasingly common, in part because scientists now know that genes are not the only authors of inheritance."); Laura Beil, *Medicine's New Epicenter? Epigenetics*, Cure (Winter 2008), http://www.curetoday.com/index.cfm/fuseaction/article.show/id/2/article_id/949 (last visited Jan. 29, 2013).

These new findings have critical impacts on our understanding of BRCA1-2. First, no researcher claims that the patented genes "cause" breast cancer. There appears to be a statistical "association" between incidences of hereditary breast cancer and these genes.[5] Since both genes are believed to be related to tumor suppression, this may account for the percentage association with breast cancer; however the mechanism by which such tumor suppression is accomplished remains a mystery, as do the gene "defects" that contribute to breast cancer risk. Not surprisingly given this lack of scientific understanding, virtually all studies reporting this association of BRCA1-2 with incidences of hereditary breast cancer have called for more research to verify the extent of the association and its actual biological basis. *See, e.g.*, Andrea Veronesi et al., *Familial Breast Cancer: Characteristics and Outcomes of BRCA 1-2 Positive and Negative Cases*, 5 BMC Cancer 70 (2005); Hannaleena Eerola et al., *Survival of Breast Cancer Patients in BRCA1, BRCA2, and NON-BRCA1/2 Breast Cancer Families: A Relative Survival Analysis from Finland*, 93 Int'l J. of Cancer 368, 368-72 (2001); Mario Budroni et al., *Role of BRCA2 Mutation Status on Overall Survival Among Breast Cancer Patients from Sardinia*, 9 BMC Cancer 62 (2009); Mahmond El-Tamer et al., *Survival and Recurrence After Breast Cancer in BRCA 1/2 Mutation Carriers*, 11 Annals of Surgical Oncology 157, 157-64 (2004); Colin B. Begg et al., *Variation of Breast Cancer Risk Among BRCA1/2 Carriers*, 299 JAMA 194, 194-201 (2008); Mary-Claire King et al., *Breast and Ovarian Cancer Risks Due to Inherited Mutations in BRCA1 and BRCA2*, 302 Sci. 643, 643-46 (2003); A. Antoniou et al., *Average Risks of Breast and Ovarian Cancer Associated with BRCA1 or BRCA2 Mutations Detected in Case Series Unselected for Family History: A Combined Analysis of 22 Studies*, 72 Am. J. of Human Genetics 1117, 1117-30 (2003). A disclaimer on NIH's National Cancer Institute webpage states the problem plainly: "no data are available from long-term studies of the general population comparing cancer risk in women who have harmful *BRCA1* or *BRCA2* mutations with women who do not have such mutations." Nat'l Cancer Inst., NIH, *supra* note 5 (emphasis added).

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[5] According to the National Institute of Health (NIH), in certain American populations BRCA1-2 mutations relate to 5–10% of all breast cancer and 10–15% of ovarian cancer. Nat'l Cancer Inst., NIH, *BRCA1 and BRCA2: Cancer Risk and Genetic Testing*, http://www.cancer.gov/cancertopics/factsheet/Risk/BRCA (last visited Jan. 29, 2013).

Adding to the confusion is a 2008 study demonstrating that high-risk women who did not have BRCA1-2 had a risk of new cancerous lesions considerably greater than those who were positive for the genes. Elizabeth Feldman et al., *The Incidence of Occult Malignancy and Atypical Histopathology in Prophylactic Mastectomy Specimens After Uninformative BRCA Testing*, 9 Am. Soc'y of Breast Surgeons Official Proc. 46 (2008), https://www.breastsurgeons.org/docs/ASBrS_Proceedings_2008.pdf (last visited Jan. 29, 2013). As with the association to cancer, these seemingly contradictory conclusions need further research to be better understood.

However, both beneficial testing and further research are stymied by gene patents. *See* Dep't of Health and Human Servs. (DHHS), *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests* 2 (Apr. 2010) ("[T]here is evidence to suggest that patents on genes discourage follow-on research. . . . [W]hen exclusive rights are successfully enforced, there is only one provider of a genetic test, such as in the case of genetic testing for breast cancer . . . ."); Heidi Williams, *Intellectual Property Rights and Innovation: Evidence from the Human Genome* (Nat'l Bureau of Econ. Research, Working Paper No. 16213, 2010) ("Taken together, these results suggest that Celera's [two-year intellectual property] had persistent negative effects on subsequent innovation relative to a counterfactual of Celera genes having always been in the public domain."); Robert Cook-Deegan et al., *The Dangers of*

Diagnostic Monopolies, 458 Nature 405, 405-06 (2009).

In sum, our emerging understanding of the role that genes and the other biological elements play in the cell, and how the environment influences those elements, indicates that the old, mechanistic, and overly-simplistic view of genes "causing" complex diseases such as cancer are simply wrong. Research now shows that many cancer cells have no genetic mutations at all. *See, e.g.*, Beil, *supra*. Instead, it is now understood that many human diseases are caused by complex dynamics between non-hereditary proteins, DNA, RNA, the cellular environment, and the extra-human environment. For example, some serious inherited diseases are likely caused by inherited bacteria, which interact with human genes in ways that are scarcely understood today. Economist, *supra*. Thus by allowing the patenting of one product of nature's "building blocks" in this overall process, research into this complex and dynamic process is halted. DHHS, *supra*, at 3 ("[P]atents on genes and associations threaten the development of new and promising testing technologies . . . . These concerns are more than hypothetical. Patents are already hindering the development of multiplex tests.").[6]

Just as billions of dollars of government research have shown the gene is not "the dictator" of heredity and hereditary diseases, patents on genes such as the BRCA1-2 halt the progress of this new scientific paradigm; they halt the investigation of how these DNA sequences interact with other biological elements, which may be far more important than the genes with regard to disease creation. *See Mayo*, 132 S. Ct. at 1294 (in determining Section 101 eligibility, considering whether the patents risk "disproportionately tying up the use of the underlying natural laws, inhibiting their use in making further discoveries"); *id.* at 1301 ("The Court has repeatedly emphasized this last mentioned concern, a concern that patent law not inhibit further discovery by improperly tying up the future use of laws of nature."). Halting science's critical march into a more comprehensive understanding of disease causation, and nature more broadly, is flatly contrary to patent law's basic purpose, to "promote the Progress of Science and useful Arts." U.S. Const. art. I, § 8, cl. 8; *Chakrabarty*, 447 U.S. at 307, 315.

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[6] *See also* DHHS, *supra*, at 2 ("Moreover, patents on genes are not needed to stimulate the disclosure of research discoveries. . . [DHHS's expert committee] found no cases in which possession of exclusive rights was necessary for the development of a particular genetic test . . . .").

B. The Privatization of Genetic Heritage Violates the Fundamental Common Law Precepts of Common Heritage, the Public Domain, and the Public Trust.

The genetic building blocks of life and its elements are the common heritage of humanity, available to all to learn from and utilize. Gene patents are antithetical to the tenets of common heritage, the public domain, and the public trust. As naturally-occurring resources that are central to human identity and survival, genes are part of the common heritage of humanity and should be held as part of the public trust, owned by all people, not granted to a single firm to the exclusion of all others.

Patents should not be granted for genes because genes are *res communis*, the common heritage and inheritance of mankind. The information that genes embody is "part of the storehouse of knowledge of all men." *Funk Bros.*, 333 U.S. at 130. Pursuant to the common heritage theory, public resources such as genes are available for use by all without restriction, for the benefit of humanity. U.N. Educ., Scientific and Cultural Org., Universal Declaration on the Human Genome and Human Rights, 29th Sess., 29C/Res. 19, at art. 12(a) (Nov. 11, 1997) ("Benefits from advances in biology, genetics and medicine, concerning the human genome, shall be made available to all, with due regard for the dignity and human rights of each individual."); *see also* Linda J. Demaine & Aaron Xavier Fellmeth, *Reinventing the Double Helix: A Novel and Nonobvious Reconceptualization of the Biotechnology Patent*, 55 Stan. L. Rev. 303, 442 (Nov. 2002) ("Scores of eminent scientists and many foreign governments have taken the position that the human genome . . . [is] the common heritage and inheritance of mankind . . . ."); Pilar N. Ossorio, *The Human Genome as Common Heritage: Common Sense or Legal Nonsense?*, 35 J.L. Med. & Ethics 425, 426-30 (2007); Melissa L. Sturges, *Who Should Hold Property Rights to the Human Genome? An Application of the Common Heritage of Humankind*, 13 Am. U. Int'l L. Rev. 219, 245-52 (1997); Barbara Looney, *Should Genes Be Patented? The Gene Patenting Controversy: Ethical and Policy Foundations of an International Agreement*, 26 Law & Pol'y Int'l Bus. 231, 231-72 (1994); Hubert Curien, *The Human Genome Project and Patents*, 254 Sci. 1710, 1710-12 (1991).

The common heritage doctrine has been applied in many other areas, to a variety of resources, including the sea floor, activities in outer space, the use of seeds, preservation of historical artifacts, and the conservation of environmental resources. *See, e.g.*, Kernal Baslar, *The Concept of the Common Heritage of Mankind in International Law* 31-37, 108-109 (1998); Andrew Chin, *Research in the Shadow of DNA Patents*, 87 J. Pat. & Trademark Official Soc'y 846, 864 (Nov. 2005); *see also* Emmanuel Aguis, *Germ-Line Cells—Our Responsibilities for Future Generations* 133-143 (Salvino Busuttil ed., 1990) ("If there is an obvious component of the common heritage of mankind, indeed, more obvious than the resources of the sea-bed itself, it is the human genetic system.").[7]

Similarly, the importance of the public domain is recognized in patent law by the exclusion of the laws of nature, natural phenomena, and abstract ideas from patent eligibility. *Mayo*, 132 S. Ct. at 1293. This Court has long held that existing knowledge and materials that exist in the public domain are not to be patented: "Congress may not authorize the issuance of patents whose effects are to remove existent knowledge from the public domain, or to restrict free access to materials already available." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 6 (1966); *see also Bonito Boats, Inc. v. Thunder*

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[7] Because of the unique legal status of indigenous peoples and their rights to their genetic material, *see infra*, the doctrine of common heritage of mankind is not applicable to them. Accordingly, specific legislation and regulations are needed to reserve the right of indigenous peoples to determine whether or not they want to provide their genetic material for research purposes.

Craft Boats, Inc., 489 U.S. 141, 151 (1989) (explaining that "free exploitation of ideas will be the rule, to which the protection of a federal patent is the exception"); *Precision Instrument Mfg. Co. v. Auto. Maint. Mach. Co.*, 324 U.S. 806, 816 (1945) ("[A] patent is an exception to the general rule against monopolies . . . .").

"A patent by its very nature is affected with a public interest." *Precision Instrument*, 324 U.S. at 816. By preventing research and monopolizing genetic data, gene patents take information out of the public domain and impede the progress of science, contrary to the express intent of the Constitution. U.S. Const. art. I, § 8, cl. 8; *Mayo*, 132 S. Ct. at 1293 (warning against the "monopolization" of "basic tools of scientific and technological work" through patents); *In re Marden*, 47 F.2d at 959 (holding that "pure vanadium is not new in the inventive sense, and it being a product of nature, no one is entitled to a monopoly of the same").

Finally, the related concept of the public trust doctrine also illustrates why human genetics should be protected as public property. *See, e.g.*, Looney, *supra*. The public trust doctrine requires governments to hold property in trust for use by the general public, and maintain that property for certain types of public uses. *See generally* Joseph L. Sax, *The Public Trust Doctrine in Natural Resources Law: Effective Judicial Intervention*, 68 Mich. L. Rev. 471, 475-83, 485-89, 556-57 (1970). The conceptual underpinnings of the public trust doctrine are: that certain interests are so intrinsically important to every citizen that their free availability tends to mark the society as one of citizens rather than serfs;

that certain benefits derive so directly and particularly from nature that they should be available to the entirety of a populace; and that certain uses of property have value only to the extent that they are public. *Id.* As such, the public trust doctrine should apply here to cover genes, because genes are of intrinsic importance to all people and their benefits flow directly from human biology, the value of which is severely negated if not public. *See, e.g.*, Ossorio, *supra*, at 427.[8]

Accordingly, human genetic information should remain in the public domain, held in public trust, in order to prevent the monopolization of our common heritage.

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[8] In addition to violating basic rights common to humanity, gene patents cause the underutilization of genetic material. The proliferation of intellectual property rights on original genetic material may stifle life-saving innovations downstream from product research and development, a phenomenon known as "the tragedy of the anticommons." *See, e.g.*, Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 Sci. 698, 698-701 (1998) (citing Michael A. Heller, *The Tragedy of the Anticommons: Property in the Transition from Marx to Markets*, 111 Harv. L. Rev. 621, 621-88 (1998)); Chin, *supra*, at 878-79. If the right of companies to exclude others from use of genetics continues and expands, all genetic resources will become increasingly underutilized, reducing the benefit of these resources to humanity.

C. Gene Patents Facilitate the Exploitation of Indigenous Peoples and Violate International Law.

Genes are fundamentally storehouses of information that have been passed down to each person from his or her ancestors, and that will be passed down to his or her children. For Indigenous groups, their genetic materials hold traditional, cultural, and spiritual significance. *See, e.g.*, Debra Harry & Le'a Malia Kanehe, *Asserting Tribal Sovereignty Over Cultural Property: Moving Towards Protection of Genetic Material and Indigenous Knowledge*, 5 Seattle J. for Soc. Just. 27, 32-33 (2006) ("Several Indigenous peoples recognize an inherent sacredness in DNA.").

The legality of gene patents has caused some to view Indigenous peoples as "treasure troves." Researchers have applied for patents based on cell lines derived from Indigenous people without their consent, such as the Guyami of Panama, the Hagahai of Papua New Guinea, and the Melanese of the Solomon Islands. *See, e.g.*, Debra Harry, *Indigenous Peoples and Gene Disputes*, 84 Chi.-Kent L. Rev. 147, 179-182 (2009). Indigenous communities are attractive to genetic researchers for several reasons, including: 1) they are perceived to be more genetically homogenous than other populations, making it easier for researchers to find links between specific diseases and genetic sequences; and 2) they often have high rates of specific diseases such as type II diabetes, heart disease, cancers, and arthritis. *See, e.g.*, Rebecca Tsosie, *Cultural Challenges to Biotechnology: Native American Genetic Resources and the Concept of*

Cultural Harm, 35 J.L. Med. & Ethics 396, 396, 405 (2007).

The legal battle between members of the Havasupai Tribe and Arizona State University demonstrates the research interests in Indigenous peoples' genes, and the failure of the current legal and ethical framework to respect the significance of such materials to Indigenous peoples. Members of the Havasupai, a tribe from an isolated region of the Grand Canyon in Arizona, were sought as research subjects to study the possibility of a genetic basis for the prevalence of type II diabetes within the Tribe. Although the Tribe and some members consented to diabetes-related research at Arizona State University, their blood samples were used for other purposes—including inbreeding, schizophrenia, and ancient migration theories—and also transferred to other universities, all without their consent. *See, e.g.*, Katherine Drabiak-Syed, *Lessons from Havasupai Tribe v. Arizona State University Board of Regents: Recognizing Group, Cultural, and Dignitary Harms as Legitimate Risks Warranting Integration into Research Practice*, 6 J. Health & Biomed. L. 175, 175-86 (2010). The Tribe and individual members maintained that the defendant university and researchers "violated the Havasupai Tribe's and tribal members' cultural, religious, and legal rights and have caused the Havasupai Tribe and its members severe emotional distress." *Havasupai Tribe v. Ariz. Bd. of Regents*, 204 P.3d 1063, 1069 (Ariz. Ct. App. 2008), *appeal denied*, 2009 Ariz. LEXIS 82 (Apr. 20, 2009). The parties ultimately settled, requiring the defendants to return all of the Tribe's genetic materials as well as terminate any ongoing or new research using the

Tribe's genetic materials. *See* Drabiak-Syed, *supra*, at 195.

This type of genetic research on Indigenous peoples often results in patents. For example, the U.S. Patent and Trademark Office granted the NIH and DHHS a patent on a human T-cell line obtained from a Hagahai man, a member of an isolated tribe of Papua New Guinea, without his consent. Harry, *supra*, at 180; *see also* U.S. Patent No. 5,397,696 (issued Mar. 14, 1995). NIH eventually forfeited its patent rights, but only after an international uproar. *See, e.g.*, Gary Taubes, *Scientists Attacked for "Patenting" Pacific Tribe*, 270 Sci. 1112, 1112 (1995); Sally Lehrman, *U.S. Drops Patent Claim to Hagahai Cell Line*, 384 Nature 500, 500 (1996); Eric L. Kwa, *In the Wake of the Hagahai Patent: Policy and Legal Development on Gene Ownership and Technology*, *in Pacific Genes & Life Patents* (Aroha Te Pareake Mead & Steven Ratuva eds., United Nations Univ. Inst. of Advanced Studies 2007).

The "Guayami patent" is another example. In that case the U.S. Department of Commerce filed a patent application for "Human T-Lymphotropic Virus Type II from Guayami Indians in Panama," even though neither the tribe nor the woman whose genetic sequence was at issue knew anything about the development of the cell line or the patent application. *See, e.g.*, Marina L. Whelan, *What, If Any, Are the Ethical Obligations of the U.S. Patent Office? A Closer Look at the Biological Sampling of Indigenous Groups*, 2006 Duke L. & Tech. Rev. 14, 13-15 (2006). The President of the Guayami General Congress wrote the U.S. Secretary of Commerce, demanding that the application be withdrawn because it was made without consultation or consent and because the patent was "not an invention but rather a discovery of an antibody which is part of the blood of a Guayami woman." *Id.* As a result of this protest from the Guayami people as well as from numerous public interest groups, the patent was withdrawn. *Id.*

Although the U.S. government elected to drop its patents on the Hagahai and Guayami genes due to public and diplomatic pressure, there was not any legal obligation to so act. Indigenous peoples remain vulnerable to similar patents on their genes, particularly following the 1980 passage of the Bayh-Dole Act, which encourages universities to patent inventions developed with federal funding. Patent and Trademark Law Amendments Act, Pub. L. No. 96-517 (1980) (codified as amended in scattered sections of 35 U.S.C.). This legislation has facilitated the entry of universities into the marketplace by giving them the right to patent and commercialize inventions, including human genes.

The United Nations Declaration on the Rights of Indigenous Peoples, adopted in 2007 by the U.N. General Assembly, recognizes that "Indigenous peoples have the right to maintain, control, protect and develop their cultural heritage, . . . including human and genetic resources . . . ." United Nations Declaration on the Rights of Indigenous Peoples, G.A. Res. 61/295, U.N. GAOR, 61st Sess., U.N. Doc. A/RES/61/295, at art. 31 (Sept. 13, 2007). This right stems from the central right of self-determination, which includes a right to autonomy or self-government in matters relating to internal or local affairs. *Id.* at art. 4. In the United States, this right is embodied through the recognition and exercise of tribal sovereignty for federally-recognized tribes. *See* Tsosie, *supra*, at 401-09. While the proper utilization and disposition of genetic material associated with a tribe is an internal matter, there is no requirement in federal law to protect this right. *Id.* at 408 ("[L]egal categories of property rights and privacy rights inadequately address the claims being expressed by Native people with respect to human remains, bodily materials, and the intangible components associated with study or research that generates information and knowledge about these remains and materials.").

The U.N. Declaration also recognizes the obligation upon States to obtain the free, prior, and informed consent (FPIC) of indigenous peoples when legislative or administrative actions may affect them, as well as prior to the extraction of their resources. G.A. Res. 61/295 at arts. 19 & 32.[9] Given the demonstrated history of exploitation of Indigenous peoples' genetic material without their informed consent, any extension of patent protection to genes obtained from Indigenous peoples without their FPIC is an infringement of their internationally-recognized rights.

Hence, properly excluding gene sequences as impermissible subject matter pursuant to the product of nature doctrine would serve to protect the rights of Indigenous peoples under international and federal law that are currently being violated.

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[9] This principle of international law is closely related to the rights of individual human research subjects and patients to informed consent under federal law, except that FPIC is a right uniquely applicable to Indigenous peoples as collective groups, rather than as individuals.

D. Gene Patents Facilitate the Violation of Patients' Rights to Informed Consent.

Finally, the pernicious practice of granting gene patents facilitates the violation of basic notions of informed consent. Genetic research is being undertaken on people without their consent, as researchers prospect for genes.[10] Informed consent requires disclosure of all the information that is material to a patient's intelligent and informed decision. *See, e.g.*, *Johnson v. Kokemoor*, 545 N.W.2d 495, 501 (Wis. 1996). Justice Cardozo was one of the first to acknowledge the existence of a basic right to informed consent, concluding that "[e]very human being of adult years and sound mind has a right to determine what shall be done with his own body." *Schloendorff v. Soc'y of New York Hosp.*, 105 N.E. 92, 93 (N.Y. 1914), *overruled on other grounds by Bing v. Thunig*, 143 N.E.2d 3, 8 (N.Y. 1957). The concept is "fundamental in American jurisprudence." *Canterbury v. Spence*, 464 F.2d 772, 780 (D.C. Cir. 1972). Yet the patenting of genes allows private parties to own others' physical makeup without their consent or knowledge.

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[10] Press Release, U.N. Educ., Scientific and Cultural Org., Ethical Guidelines Urgently Needed For Collecting, Processing, Using and Storing Human Genetic Data, U.N. Press Release No. 2002-93 (Nov. 24, 2002), *available at* http://portal.unesco.org/en/ev.php-URL_ID=7791&URL_DO=DO_PRINTPAGE&URL_SECTION=201.html (last visited Jan. 29, 2013).

Researchers and health care institutions have litigated to gain ownership of patients' cell lines, tissue, and genes in order to commercialize them, over the patients' objections. *See, e.g.*, *Moore v. Regents of the Univ. of Cal.*, 793 P.2d 479 (Cal. 1990); *Wash. Univ. v. Catalona*, 490 F.3d 667 (8th Cir. 2007). In *Moore*, the seminal case regarding an individual's right to informed consent, the patient suffered from hairy-cell leukemia. 793 P.2d at 481. Before advising Moore that he needed to have his spleen removed, his physician decided that he would use Moore's spleen for research purposes. *Id.* The physician did not disclose his research intentions when he suggested Moore undergo surgery and later derived a cell line from Moore's T-lymphocytes, valued at $3 billion, over which the University of California applied for a patent. *Id.* Moore sued, arguing that he was unable to make an informed decision about whether to undergo his surgery because he was unaware of his physician's ulterior motives. *Id.* at 482. The California Supreme Court agreed, holding that "a physician must disclose personal interests unrelated to the patient's health, whether research or economic, that may affect the physician's professional judgment." *Id.* at 483. However the *Moore* decision has been limited to physicians and other individuals with whom a patient shares a fiduciary relationship—not to researchers and donors, even when the intent to patent and commercialize is not disclosed. *See Greenberg v. Miami Children's Hosp. Research Inst., Inc.*, 264 F. Supp. 2d 1064, 1067-68, 1070-71 (S.D. Fla. 2003) (distinguishing *Moore* in case in which a researcher patented the genetic sequence for Canavan disease after studying the blood and tissue samples of several donors).

NIH studies show that the public believes robust informed consent should be required. *See* Juli Murphy et al., *Public Perspectives on Informed Consent for Biobanking*, 99 Am. J. Public Health 2128, 2128-34 (2009). Yet the perverse incentives of gene patents weaken researcher commitment to openness. Leili Fatehi & Ralph Hall, *Enforcing the Right of Human Sources to Informed Consent and Disclosures of Incidental Findings from Biobanks and Researchers: State Mechanisms in Light of Broad Regulatory Failure*, 13 Minn. J. L. Sci. & Tech. 575, 579, 579 n.8, 581 (2012) (explaining the use of loopholes by DNA repositories "so that no obligations to human sources may exist").[11] The situation is exacerbated by a "broad regulatory failure" to protect informed consent requirements at a federal level, forcing states to take up the task. *Id.* at 582-84.[12] So long as genes remain patentable, litigation and uncertainty will flourish and multiply. *See id.* at 607-52 (discussing the many unanswered state and common law questions).

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[11] *See also Grimes v. Kennedy Krieger Inst., Inc.*, 782 A.2d 807, 851 (Md. 2001) ("There is thus an inherent reason for not conveying information to subjects as it arises, that might cause the subjects to leave the research project. That conflict dictates a stronger reason for full and continuous disclosure.").

[12] *See* R. Hakimian et al., Nat'l Cancer Inst., NIH, *50-State Survey of Laws Regulating the Collection, Storage, and Use of Human Tissue Specimens and Associated Data for Research*, available at http://www.cancerdiagnosis.nci.nih.gov/humanSpecimens/survey/ (last visited Jan. 29, 2013); *see, e.g.*, *Bearder v. Minnesota*, 806 N.W.2d 766 (Minn. 2011) (holding that state agency's practice of collecting, using, storing, and disseminating children's blood samples and test results without obtaining written informed consent violated the state's Genetic Privacy Act).

CONCLUSION

For the foregoing reasons, the patent claims should be held invalid.

Respectfully submitted,

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January 31, 2013

AMICUS
CURIAE
BRIEF

FILED
[illegible]

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF *AMICUS CURIAE* INVITAE CORPORATION IN SUPPORT OF PETITIONERS

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INTEREST OF *AMICUS CURIAE*[1]

InVitae Corporation ("InVitae") is a San Francisco, California-based company providing genetic testing and genome management services based on human DNA sequencing. InVitae's goal is to aggregate all the world's genetic tests into a single assay with higher quality, faster turn-around time, and at a lower cost than most single gene tests performed today. InVitae is one of many companies in a rapidly evolving industry utilizing advances in massively parallel DNA sequencing to analyze large numbers of genes, as well as to sequence whole genomes or large regions of the genome for diagnostic purposes. *See, e.g.*, Tracy Tucker et al., *Massively Parallel Sequencing: The Next Big Thing in Genetic Medicine*, 85 Am. J. Hum. Genet. 142, 142 and 148-152 (2009), available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2725244/. The future and promise of personalized medicine rests on the ability of medical practitioners to access comprehensive information about patients' genetic information, including whether a patient possesses clinically relevant variations in any of a broad panel of human genes. *Id.*

Since the 1990s when the sequencing of the first full human genome began, the technologies and chemistry available for genomic sequencing have evolved rapidly. While the first genome was sequenced at a cost of $437 million over 13 years,[2] today's widely available "Next Generation" methods can, with a single laboratory assay, sequence the genome of an individual patient in a few days at costs of around $5,000 - $10,000, and sequencing subsets of a patient's genes or the complete set of roughly 20,000 genes (called "the exome") cost well below $1,000 today.[3] Current estimates suggest that these prices will continue to decline rapidly thereby greatly expanding the uses and market for large scale DNA sequencing. *See, e.g.*, Matthew Harper, ***Biotech Firms Battle Over Same Day Genomes***, Forbes Magazine, January 10, 2012, available at http://www.forbes.com/sites/matthewherper/2012/01/10/biotech-firms-battle-over-same-day-genomes; Christianne Bird, *Next-Gen Sequencing Services: An Expanding Role in Clinical Applications Opens New Markets*, Genet. Eng'g & Biotech. News, May 1, 2012, http://www.genengnews.com/gen-articles/next-gen-sequencing-services/4088/; Ivan Karabaliev, *The $1,000 Genome is Almost Here—Are We Ready?*, Scientific American, Oct. 15, 2012, http://blogs.scientificamerican.com/guest-blog/2012/10/15/the-1000-genome-is-here-are-we-ready. Comprehensive genetic information has become both affordable and easily available to clinicians and researchers to help them improve human health.

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[1] No person other than the *amicus curiae* or their counsel has made any monetary contribution to the preparation or submission of this brief. Further, no counsel for any party authored this brief in whole or in part. Petitioners have lodged a blanket consent to the filing of amicus briefs, and a letter of consent to the filing of this brief by Respondents has been lodged with the Clerk of the Court.

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[2] *E.g.*, U.S. Dept. of Energy Genome Programs, Human Genome Project Information (2004), http://www.ornl.gov/sci/techresources/Human_Genome/project/budget.shtml.

[3] Some observers have likened the exponentially rapid pace of change in the speed and cost reduction for genomic sequencing technology to Moore's Law which states that "[t]he number of transistors on a [semiconductor] chip will double approximately every 24 months." *See, e.g.*, Moore's Law and Intel Innovation, http://www.intel.com/content/www/us/en/silicon-innovations/moores-law-consumer-technology.html; National Human Genome Research Institute, Cost per Genome (2012), http://www.genome.gov/images/content/cost_per_genome.jpg.

Current commercially available genomic sequencing technologies achieve such great improvements in speed and efficiency through massively parallel processes. *See, e.g.*, Tucker, *supra* at 142. A patient's genetic information is determined by collecting a sample of the patient's DNA, breaking those DNA molecules into millions of fragments and simultaneously copying and sequencing all or some of those fragments side by side. *Id.* at 142-144. InVitae is concerned that patents claiming individual human genes or fragments of such individual human genes, if asserted, could impair a patient's ability to have his or her own relevant genetic information sequenced for use in connection with the patient's own medical care. A patent holder might claim that one of those millions of gene fragments being sequenced is putatively covered by a claim to a specific gene fragment. Worse, in the circumstance in which there are multiple distinct patentees each claiming a different gene, any one patentee could threaten to prevent the sequencing of a patient's exome or entire genome because such sequencing necessarily includes sequencing each human gene contained in the human genome. Worse yet, within any individual gene there could be hundreds or even thousands of individual mutations identified and separately patented as they are discovered so that no single patentee could permit the sequencing of such a gene. No patent should foreclose an individual's right to self-knowledge of their own genetic information.

InVitae is a strong believer in the importance of a vital U.S. patent system. Nonetheless, InVitae is concerned that some patentees holding patent claims on specific genes or on individual mutations within a gene could foreclose its ability to provide patients with access to their genetic information which is naturally present in the human genome as well as preventing the research and commercial life sciences communities from developing further understanding of the medical significance of aspects of that genetic information. A circumstance in which myriads of genes and variations in the human genome are privatized through separate patents could substantially impair the development of the genomic testing industry and erode U.S. competitiveness in a critical area of healthcare innovation.

SUMMARY OF ARGUMENT

The human genome is constituted of human genes and other related sequences which are naturally occurring information. With respect to a human gene, such information includes the normal (or wild type) sequence as well as common and uncommon variants of the sequence and associations between such variations and medical conditions or predispositions. This Court has long held that laws of nature and pre-emption of their use are not patentable subject matter. *E.g.*, *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289, 1294-1295 (2012). Human genetic information, including sequences of human genes, gene fragments and correlations between variations in human genes and medically relevant patient information all constitute laws of nature akin to the correlation between drug metabolite concentrations measured in a patient and the determination of the suitable drug dosage for that patient which was found to be a law of nature under the *Mayo* test for patentable subject matter. *Id.* at 1296-1297.

Patent claims which pre-empt the use of laws of nature in the form of human genetic information embrace patent ineligible subject matter. Even if a patent claim is directed to a gene as a composition of matter, that gene is defined in terms of its genetic sequence and it embodies a law of nature in the form of the relevant genetic sequence. Consequently, to the extent that patent claims to nucleic acids defined with respect to human gene sequences (or fragments thereof or variations therein) can pre-empt the use of a law of nature including uses such as determining a patient's genetic sequence, the patent claim is directed to unpatentable subject matter.

The opinions of the Court of Appeal illustrate a tension between (1) the majority's view of a patent claim directed to an isolated nucleic acid as a patentable composition of matter distinct from the gene in its native chromosome and (2) the dissent's view of such a claim as unpatentable in that it may pre-empt the use of a law of nature in the form of the claimed sequence information. Amicus suggests a rule of claim construction for human gene patents that would exclude as patent ineligible from the scope of a patent claim any subject matter to the extent it serves to pre-empt the use of a law of nature. Such a rule of claim construction could preserve claims to human genes, to the extent that they claim additional inventive subject matter beyond the patent ineligible law of nature—any portion of the sequence of the human gene—or otherwise cover compositions of matter in contexts where their use would not preempt a law of nature.

ARGUMENT

I. UNDER THE *MAYO* STANDARD, SEQUENCES OF HUMAN GENES AND GENE FRAGMENTS, AND VARIATIONS IN THEIR SEQUENCES, SHOULD BE CONSIDERED UNPATENTABLE LAWS OF NATURE.

The human genome is fundamentally information and DNA is simply nature's most efficient information storage and retrieval device.[4] Nucleic acids, principally DNA in the form of long sequences comprised of four nucleotide bases (adenine, thymine, guanine, and cytosine, or A, T, G and C), embody this information.[5] It consists of 23 pairs of chromosomes with each chromosome including a sequence of between approximately 50 million to 250 million base pairs long which together include approximately 20,000 human genes.[6] Each embodiment of a human gene in a human cell includes a genetic sequence providing the information necessary for the expression of a corresponding protein. Not every occurrence of a specific human gene, however, has an identical sequence and variations in those sequences can give rise to differences in the proteins expressed from those genes.

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[4] Recent reports of the encoding of the entire collection of Shakespeare's sonnets in a single DNA molecule (weighing much less than a billionth of a gram) illustrates the extraordinary data storage capacity of nucleic acids. *See, e.g.*, Ian Sample, *Shakespeare and Martin Luther King demonstrate potential of DNA storage*, The Guardian, Jan. 24, 2013, http://www.guardian.co.uk/science/2013/jan/23/shakespeare-sonnets-encoded-dna.

[5] The decisions below discuss the nature of the human genome, nucleic acids and the genetic code in some detail, and InVitae will not revisit the science here except in a summary fashion.

[6] While less than 2% of the full human genome is made up of genes, all of its 3 billion base pairs are inheritable information. *See, e.g.*, Brendan Maher, *ENCODE: The Human Encyclopedia*, Nature, Sept. 5, 2012, at 46, 46, available at http://www.nature.com/news/encode-the-human-encyclopaedia-1.11312. As its role becomes better understood, the clinical significance of the non-

Even though much of the sequence information in the human genome is consistent from person to person, there are millions of specific variations which have been identified. In an ever-increasing number of cases, these individual variations or certain collections of variations are being identified as correlating to certain diseases or increased risks of contracting certain diseases.[7] The sequences of human genes, variations and mutations in these genes observed in individual patients are all naturally occurring information. Even fragments of more than a few nucleotides in length can act as distinctive "bookmarks" within the human genome and thus serve as a tool to reference a particular gene, and consequently they too are "laws of nature" which are highly relevant to the act of sequencing their corresponding gene. Similarly, the correlations between this genetic information and medically relevant information such as diagnosis of a disease, susceptibility to certain diseases, responsiveness to certain pharmaceuticals, and likelihood of adverse reactions to certain pharmaceuticals constitute naturally occurring information. Access to this genetic information

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gene sequences to patient care may come to rival that of human genes. *Id.* at 46-48.

[7] BRAC1 and BRCA2, the subject matter of the patents at issue in the case below, are merely two examples of human genes for which certain variations have been identified as correlated with risk of certain diseases.

is becoming increasingly important in routine patient medical care as its costs have plummeted.[8]

This Court has held that while the Patent Act defines categories of patentable subject matter, 35 U.S.C. 101, laws of nature and pre-emption of their uses are nonetheless excluded. *Mayo*, 132 S. Ct. at 1294-1295 and 1302. Specifically, the Court in *Mayo* found that an observed correlation between the concentrations of certain metabolites of an administered drug in a patient and the clinical suitability of the administered dosage of that drug for that patient constituted a law of nature for the purposes of determining that patent claims directed to such correlations did not constitute patentable subject matter. *Id.*at 1296-1297. By analogy to the *Mayo* decision, human genomic information including a patient's sequence for a particular gene, the presence or absence of variations in the genetic sequence and associations between that sequence information and medically relevant consequences are all laws of nature. In comparison with the metabolite correlations at issue in *Mayo*, the sequences of human genes and information relating naturally occurring variations in human genes to diagnoses and other patient care are more fundamental and more of a law of nature than a correlation between metabolites and suitable dosage for a drug where the correlation is based upon administration of the particular drug.[9]

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[8] While the first human genome was completed in 2003 at a cost of hundreds of millions of dollars, today, just ten years later the cost is approaching a thousand dollars. *See, e.g.*, Tucker, *supra* at 142; Harper, *supra*; Karabaliev, *supra*.

[9] Other correlations with genetic information—such as use of certain genetic markers to identify patients who are suitable for a particular pharmaceutical treatment or susceptible to certain

II. PATENT CLAIMS TO HUMAN GENES, GENE FRAGMENTS AND VARIATIONS SHOULD BE CONSTRUED TO EXCLUDE AS UNPATENTABLE SUBJECT MATTER ALL GENETIC INFORMATION CONSTITUTING A LAW OF NATURE

Patent claims directed to human genes are frequently drafted such that the sole distinctive feature of the claim is the sequence of the gene or a fragment of the gene.[10] While such human gene claims are styled as claims to a composition of matter or molecule such as an "isolated gene" having a particular genetic sequence or an "isolated nucleic acid" having a particular genetic sequence, the defining characteristic of such human gene claims is presented with reference to the genetic sequence information embodied by such a molecule. In its holding below, the Federal Circuit majority emphasized the distinction between an isolated nucleic acid molecule having a sequence for a human gene (or a fragment of a human gene) and the same sequence as it appears naturally within a human chromosome. *Ass'n for Molecular Pathology v. U.S. P.T.O.*, 689 F.3d 1303, 1341-1344 (Fed. Cir. 2012). The majority's reliance upon the isolation of a claimed gene or gene fragment fails to account for the fact that such a claim to an isolated

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adverse effects of certain pharmaceuticals—would constitute correlations which are laws of nature analogous to the correlation found to be a law of nature in the *Mayo* decision.

[10] Such gene sequences are typically defined in terms of a sequence of nucleotides or a sequence of amino acids for which the gene codes. By way of illustration, Claim 1 of U.S. Patent 5,747,282 reads as follows: "1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2." 2J.A. 821.

gene may nonetheless be exploited to pre-empt a law of nature—the human gene sequence it embodies.

The pre-emptive effect of a patent claim is measured by the properly construed scope of the claim in the context of the statutorily defined categories of activities which constitute patent infringement. *See, e.g.*, ***Markman v. Westview Instruments, Inc.***, 517 U.S. 370, 372-374 (1996). The Patent Act provides that the activities of, *inter alia*, making or using a claimed composition of matter constitute patent infringement. 35 U.S.C. 271. Consequently, activities involving the making or using of an isolated nucleic acid having the sequence of a claimed human gene (or human gene fragment) in the course of determining a patient's genetic sequence could be asserted to pre-empt the use of such a law of nature. For example, the determination of a patient's genetic sequence typically entails the steps of extracting genetic material from a biological sample (blood, saliva, biopsy, etc.) from the patient, digesting the genetic material into numerous fragments, selecting some or all of the fragments for analysis, making copies of the selected fragments and then reading the sequences of the fragments. Using a claim covering an isolated human gene fragment to stop the making of copies of such fragments and the using of such fragments in the course of determining a patient's genetic sequence information would pre-empt the use of a law of nature and therefore should be excluded from the patentee's monopoly provided by a patent. By contrast, to the extent that a claim referencing a human gene includes other inventive subject matter and/or does not serve to pre-empt the exploitation of a law of nature such other subject matter should remain patent eligible subject to the other requirements governing patent eligibility under 35 U.S.C. 101 and this Court's precedents.

CONCLUSION

For the foregoing reasons, the *amicus curiae* InVitae Corporation respectfully suggests that the Court consider (i) adopting a rule of construction of patent claims to exclude from the scope of the claims that subject matter which serves to pre-empt the use or exploitation of a law of nature and (ii) confirming that human genetic information, including sequences, variations and correlations between such variations and medical consequences thereof, all constitute patent ineligible laws of nature.

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January 31, 2013

AMICUS
CURIAE
BRIEF

RECORD
AND
BRIEFS

No. 12-398

Supreme Court, U.S.
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On Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

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BRIEF OF THE JUHASZ LAW FIRM, P.C. AS AMICUS CURIAE SUPPORTING NEITHER PARTY

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QUESTION PRESENTED

Are human genes patentable?

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INTEREST OF AMICUS CURIAE[1]

The author of this brief is a registered patent practitioner with law and science degrees and is a member of the patent firm The Juhasz Law Firm, P.C. Paul R. Juhasz has been practicing for 29 years and holds a B.S.Chem.E., a B.S.E.E., a J.D., and a P.E. Paul R. Juhasz deals with the issue of subject matter patentability for clients of the Firm on a regular basis. Mr. Juhasz has written extensively and is extensively published on the Supreme Court's *Bilski* and *Mayo* decisions and subject matter patentability under 35 U.S.C. § 101. This brief is filed solely on behalf of the Firm and not on behalf of clients of the Firm. Amicus represent neither party in this action, and offer the following views based on extensive experience on this matter.

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[1] Pursuant to Sup. Ct. R. 37.6, amicus note that no counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than amicus curiae made a monetary contribution to its preparation or submission. Petitioners and Respondents have provided written consent pursuant to Rule 37, Sect. 3(a) of the Rules of the Supreme Court of the United States to the filing of this amicus brief in this case. A courtesy notice of this filing was provided to both Petitioners and Respondents.

SUMMARY OF ARGUMENT

The Federal Circuit incorrectly held that respondent's patent claims are directed to patent-eligible subject matter.

I. The Federal Circuit failed to properly consider whether isolated DNA is an invention or discovery under this Court's *Mayo* and *Funk Bros.* decisions.

II. Isolated DNA is "new" and "useful" under *Chakrabarty*; but more is required under § 101 for the isolated DNA to be patent eligible and it is there that isolated DNA fails.

III. Preemption is the touchstone of an "invention" or "discovery" under this Court's *Mayo* and *Funk Bros.* decisions.

IV. The "engineering at the edges of DNA" for "packaging" of natural DNA does not create the quality in the recited isolated DNA useful for diagnostic targeting which is the work of nature. Those qualities of DNA are not an "invention" or "discovery" under this Court's *Mayo* and *Funk Bros.* decisions for patents cannot issue for the discovery of this phenomenon of nature.

V. The claims which are directed to isolated sequences that are identical to naturally occurring gene sequences fall squarely within the discussion of Section IV above and are not human invention. However, the judgment of the Federal Circuit as to isolated cDNA product claims should be vacated and the case should be remanded to the United States

Court of Appeals for the Federal Circuit for further consideration of whether the packaging of the DNA SEQ into cDNA molecules is an insignificant extra-solution activity or "human invention" deserving of a patent.

VI. The Court should clarify that preemption in isolated DNA arises not from isolated DNA being not "new"; rather that the isolated DNA is not an "invention" or "discovery" entitled to a patent under § 101.

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ARGUMENT

I. The Federal Circuit failed to properly consider whether isolated DNA is an invention or discovery under this Court's *Mayo* and *Funk Bros.* decisions

On Friday, November 30, 2012, the Supreme Court granted the petition of Association for Molecular Pathology, et al. for a writ of certiorari.

This is the second time that this case is before this Court. The first time, this Court remanded the case to the Federal Circuit for reconsideration in light of *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012). This time, the certiorari has been limited to the following question "Are human genes patentable?"

On remand, the Federal Circuit once again decided the subject matter patentability of the isolated DNA claims under *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), effectively "cleaving" out the analytical backbone of this Court's *Mayo* case from its decision upholding the subject matter patentability of isolated DNA. *Ass'n for Molecular Pathology v. U.S. P.T.O.*, 689 F.3d 1303, 1325 (Fed. Cir. 2012). This despite this Court's decision in *Mayo* being the reason for the remand. The District Court had invalidated the isolated DNA claims.

35 U.S.C. § 101 provides that:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

To be patent eligible subject matter, § 101 thus requires not only that the invention or discovery be "new" and "useful." § 101 also requires that the composition of matter be an "invention" or a "discovery." *Mayo, supra* at 1294 and *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 131 (1948). In *Chakrabarty*, the claimed bacterium was so "new" because of markedly different characteristics from any found in nature that the Court held the claimed bacterium to be "human invention" deserving of a patent. "His discovery is not nature's handiwork, but his own; accordingly it is patentable subject matter under § 101." *Chakrabarty, supra* at 310. Not so with *Mayo* and *Funk Bros.* where the recited claims that albeit being "new" and "useful" were found to be "nature's handiwork" and so not invention deserving of a patent. *Mayo* and *Funk Bros.*

Mayo, and its predecessor decisions, stand for the proposition that a claim taken as a whole and excluding extra-solution activity must be tailored narrowly enough to encompass only a particular application of a fundamental principle (*i.e.*, a law of nature, natural phenomena, or an abstract idea) rather than to preempt the principle itself. *Id.*; *Bilski v. Kappos*, 130 S. Ct. 3218, 3231 (2010); *Gottschalk v. Benson*, 409 U.S. 63, 72 (1972); *Parker v. Flook*, 437 U.S. 584 (1978); *Diamond v. Diehr*, 450 U.S. 175, 185 (1981). Hence, in deciding the question of patentable invention it is not enough to point to marked differences between the claimed product and products existing in nature. The question is whether those marked differences taken as a whole and excluding extra-solution activity amount to human ingenuity. *Mayo, supra* at 1294; and *Funk Bros., supra* at 131.

On remand, the Federal Circuit once again decided the patent eligibility of isolated DNA under *Chakrabarty* explaining that "the Supreme Court's decisions in *Chakrabarty* and *Funk Bros.* set out the primary framework for deciding the patent eligibility of compositions of matter, including isolated DNA molecules." *Ass'n for Molecular Pathology, supra* at 1326. According to the Federal Circuit, *Mayo* does not control the question of patent eligibility of isolated DNA molecules. *Id.*, at 1325 ("[t]he principal claims of the patents before us on remand relate to isolated

DNA molecules. *Mayo* does not control the question of patent-eligibility of such claims. They are claims to compositions of matter, expressly authorized as suitable patent-eligible subject matter in § 101." *Id.* See also, "[w]hile the *Mayo* decision does not control the outcome in this case, it is nonetheless instructive regarding the scope of the law of nature exception." *Id.*, concurring at 1339, 1340. "The Supreme Court's recent decision in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289, 1293 (2012) does not decide this case, but the Court's analysis is nonetheless instructive." *Id.*, dissenting at 1354.

In so deciding *Ass'n for Molecular Pathology*, the Federal Circuit has failed to properly apply the teachings of *Mayo* – and the teachings of *Funk Bros.* on "invention" as viewed through the "preemption" lens provided by *Mayo* – to the question of the patent eligibility of isolated DNA. As § 101 and this Court's *Mayo* and *Funk Bros.* decisions make clear, the patent eligibility of isolated DNA depends as much upon the isolated DNA satisfying the requirements of an "invention" or a "discovery," as it does upon the isolated DNA satisfying the requirements of being "new" and "useful." The Federal Circuit's failure to properly apply these teachings in *Mayo* and *Funk Bros.* has left it to this Court to decide whether isolated DNA is an "invention" or "discovery" under § 101.

II. Isolated DNA is "new" and "useful" under *Chakrabarty*; but more is required under § 101 for the isolated DNA to be patent eligible and it is there that isolated DNA fails

The Federal Circuit decided the subject matter patentability of the isolated DNA claims largely under *Chakrabarty*. *Ass'n for Molecular Pathology*, *supra* at 1325.

The Court in *Chakrabarty* held that a man-made, living microorganism is a patent-eligible manufacture or composition of matter within the meaning of § 101. 447 U.S. at 305, 307. The microorganisms were bacteria genetically engineered with four naturally occurring DNA plasmids. each of which enabled the breakdown of a different component of crude oil. *Id.*, at 305, 305 n.1. The bacteria, as a result, could break down multiple components of crude oil, a trait possessed by no single naturally occurring bacterium and of significant use in more efficiently treating oil spills. *Id.*, at 305, 305 n.2. The Court held that the bacteria was patentable since there was human ingenuity in creating a nonnaturally occurring manufacture or composition. The claim was "not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter – a product of human ingenuity 'having a distinctive name, character [and] use.'" 447 U.S. at 309-10, quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887).

The *Chakrabarty* Court distinguished engineered bacteria from the mixed bacterial cultures found unpatentable in *Funk Bros.* In *Funk Bros.*, the patentee discovered that certain bacterial strains associated with leguminous plants do not mutually inhibit each other. *Funk Bros.*, *supra* at 129-30. Based on that discovery, the patentee obtained a patent on a mixed culture of those non-inhibitive strains. *Id.* The *Funk Bros.* Court held that the bacteria's cooperative qualities were, "like the heat of the sun, electricity, or the qualities of metals," the "work of nature," and thus not patentable. *Id.*, at 130. The Court held the product unpatentable because the bacteria remained structurally and functionally the same as in their natural state. *Funk Bros.*, 333 U.S. at 131. By contrast, because Chakrabarty had produced "a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility," the Court held Chakrabarty's invention to be patentable. *Chakrabarty*, 447 U.S. at 310.

Hence, the Supreme Court has drawn a line between compositions that, even if aggregated in useful combinations or harnessed to exploit newly discovered properties, have similar characteristics as in nature, and compositions that human intervention has given "markedly different," or "distinctive," characteristics. *Id.* (citing *Hartranft*, 121 U.S. at 615; see also *Am. Fruit Growers v. Brogdex Co.*, 283 U.S. 1, 11 (1931)). Applying this test to the isolated DNAs in this case, the Federal Circuit held that the challenged claims are drawn to patent eligible subject matter largely because the claims cover molecules that are markedly different – have a distinctive chemical structure and identity – from those found in nature. *Ass'n for Molecular Pathology*, *supra* at 1328.

As the Federal Circuit noted based upon the evidence submitted by technical experts, isolated DNA is a free-standing portion of a larger, natural DNA molecule. *Id.* Isolated DNA has been cleaved (*i.e.*, had covalent bonds in its backbone chemically severed) or synthesized to consist of just a fraction of a naturally occurring DNA molecule. *Id.* For example, the *BRCA1* gene in its native state resides on chromosome 17, a DNA molecule of around eighty million nucleotides. Similarly, *BRCA2* in its native state is located on chromosome 13, a DNA of approximately 114 million nucleotides. *Id.* In contrast, isolated *BRCA1* and *BRCA2*, with introns, each consists of just 80,000 or so nucleotides; and without introns, *BRCA2* shrinks to approximately 10,200 nucleotides and *BRCA1* to just around 5,500 nucleotides. *Id.* Furthermore, claims 5 and 6 of the '282 patent cover isolated DNAs, *e.g.*, primers or probes, having as few as fifteen nucleotides of a *BRCA* sequence. *Id.*

Based on this record, the Federal Circuit held that *BRCA1* and *BRCA2* in their isolated states are different molecules from DNA that exists in the body. *Id.* As the court explained "isolated DNA results from human intervention to cleave or synthesize a discrete portion of a native chromosomal DNA, imparting on that isolated DNA a distinctive chemical identity as compared to native DNA." *Id.*

Where, as here, a composition is markedly different from naturally occurring compositions, it is hard to refute the Federal Circuit's finding that the isolated DNA composition satisfies the "new" prong of the "new" and "useful" prongs of § 101. To deny patent eligibility to isolated DNA on the grounds that it is not "new" would be to deny patent eligibility to many chemical compositions which are conventionally recited in the claims of chemical patents; including arguably the living microorganisms that the Court in *Chakrabarty* held to be patent eligible subject matter.

But the Federal Circuit's finding begs the question of whether the "new" and "useful" isolated DNA is "human ingenuity" as even the *Chakrabarty* Court makes clear is required and the Court's decisions in *Mayo* and *Funk Bros.* mandate. *Mayo*, *supra* at 1294; and *Funk Bros.*, *supra* at 130. As discussed in detail below, more is required for a composition to be § 101 patent eligible than for the composition to be "new" and "useful." The isolated DNA fails § 101 in these other aspects and hence isolated DNA is not patent eligible subject matter as detailed below.

III. Preemption is the touchstone of an "invention" or "discovery" under this Court's *Mayo* and *Funk Bros.* decisions

A composition which is "new" and "useful" must still satisfy the § 101 requirements of "invention" or "discovery." As explained in *Funk Bros.*, "[b]ut a product must be more than new and useful to be patented;

it must also satisfy the requirements of invention or discovery." 333 U.S. at 131. Apposite is *Mayo* ("They [our precedent decisions] insist that a process that focuses upon the use of a natural law also contain other elements or a combination of elements, sometimes referred to as an "inventive concept," sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself.) *Mayo, supra* at 1294. See also, *Parker v. Flook, supra* at 594 (1978); *Bilski, supra* at 3231. In other words, a natural law without more is not an invention that is eligible for patent under § 101.

In *Funk Bros.*, the patentee discovered that certain strains of nitrogen-fixing bacteria associated with leguminous plants do not mutually inhibit each other. 333 U.S. at 129-30. Based on that discovery, the patentee produced (and claimed) mixed cultures of nitrogen-fixing species capable of inoculating a broader range of leguminous plants than single-species cultures. *Id.* The Court held that the bacteria's cooperative qualities were, "like the heat of the sun, electricity, or the qualities of metals," the "work of nature," and thus not patentable. *Id.*, at 130. The Court also held that applying the newly discovered bacterial compatibility to create a mixed culture was not a patentable advance because no species acquired a different property or use. *Id.*, at 131.

In *Funk Bros.*, once nature's secret of the non-inhibitive quality of certain strains of the species of Rhizobium was discovered, the state of the art made the production of a mixed inoculant a simple step. *Id.*, at 132. It was not enough that the application of this newly discovered natural principle to the problem of packaging of inoculants may well have been an important commercial advance or even the product of skill. *Id.*, at 131. § 101 requires more than the creation of something "new." § 101 requires that the claimed cultures also be the product of invention. *Id.*

As the Court explained, Funk Brothers' packaging of inoculants could not be called an invention unless the discovery that certain strains of the several species of these bacteria are noninhibitive, and may thus be safely mixed, is invention; which the Court held that it was not. *Id.*, at 132. For as the Court explained "we cannot so hold without allowing a patent to issue on one of the ancient secrets of nature now disclosed. All that remains, therefore, are advantages of the mixed inoculants themselves. They are not enough." *Id.*

It is for the purpose of ensuring that the "ancient secrets of nature" and the "storehouse of knowledge of all men" are "free to all men and reserved exclusively to none" as explained by the Court in *Funk Bros.* that the Court articulated three judicially created exceptions to § 101's broad patent-eligibility principles: "'Laws of nature, natural phenomena, and abstract ideas' are not patentable." *Mayo, supra* at 1293 (quoting *Diamond v. Diehr*, 450 U.S. 175, 185 (1981)). The Court has also referred to those exceptions as precluding the patenting of mental processes, *Gottschalk v. Benson*, *supra* at 67, and products of nature, *Chakrabarty*, 447 U.S. at 313 ("[T]he relevant distinction for purposes of § 101 is . . . between products of nature . . . and human-made inventions."). The Court has explained that, although not required by the statutory text, "[t]he concepts covered by these exceptions are 'part of the storehouse of knowledge of all men . . . free to all men and reserved exclusively to none.'" *Bilski*, 130 S. Ct. at 3225 (quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)).

These judicially created exceptions provide the guidelines for use in defining the boundary line within which a product is patent eligible subject matter and outside of which a product is not. When a product falls outside this boundary line, they are "part of the storehouse of knowledge of all men . . . free to all men and reserved exclusively to none." *Bilski*, 130 S. Ct. at 3225 (quoting *Funk Bros.*, 333 U.S. at 130). But when inside, the product may qualify as patent eligible subject matter.

When the subject matter sought to be patented falls clearly inside or outside of this boundary line, the guidelines provided by the Court are easy to apply. But in some cases, where the subject matter arguably straddles that boundary line, such as may be in the case at bar, the application of these guidelines become more difficult. As Justice Frankfurter noted in his concurring opinion in *Funk Bros.*:

> It only confuses the issue, however, to introduce such terms as "the work of nature" and

> the "laws of nature." For these are vague and malleable terms infected with too much ambiguity and equivocation. Everything that happens may be deemed "the work of nature," and any patentable composite exemplifies in its properties "the laws of nature." Arguments drawn from such terms for ascertaining patentability could fairly be employed to challenge almost every patent.

Funk Bros., *supra*, concurring at 134, 135.

However, the body of law by the Court has and continues to evolve on this point. With this Court's recent decision in *Mayo*, defining where subject matter falls with respect to this boundary line has become clearer. 132 S. Ct. at 1293 (quoting *Diehr*, 450 U.S. at 185) (laws of nature, natural phenomena, and abstract ideas exceptions); *Benson*, 409 U.S. at 67 (mental processes); *Chakrabarty*, 447 U.S. at 313 (products of nature); *Bilski*, 130 S. Ct. at 3231 (abstract ideas).

As this Court explained in *Mayo*:

> Those cases warn us against interpreting patent statutes in ways that make patent eligibility "depend simply on the draftsman's art" without reference to the "principles underlying the prohibition against patents for [natural laws]." *Flook*, *supra* at 593. They warn us against upholding patents that claim processes that *too broadly preempt the use of a natural law*. *Morse*, *supra* at 112-120; *Benson*, *supra* at 71-72. And they insist that a process that focuses upon the use of a natural law also contain other elements or a

> combination of elements, sometimes referred to as an "inventive concept," sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself. *Flook*, *supra* at 594; see also *Bilski*, *supra* at 3230 ("[T]he prohibition against patenting abstract ideas 'cannot be circumvented by attempting to limit the use of the formula to a particular technological environment' or adding 'insignificant post-solution activity'" (quoting *Diehr*, *supra* at 191-192)).

(*Emphasis added*) *Mayo*, *supra* at 1294.

Mayo, and its predecessor decisions stand for the proposition that a claim taken as a whole and excluding extra-solution activity must be tailored narrowly enough to encompass only a particular application of a fundamental principle (*i.e.*, a law of nature, natural phenomena, or an abstract idea) rather than to preempt the principle itself. *Id.*; *Bilski*, 130 S. Ct. at 3231; *Benson*, 409 U.S. at 72; *Flook*, 437 U.S. at 594; and *Diehr*, 450 U.S. at 185.

In *Ass'n for Molecular Pathology*, the Federal Circuit stopped short of applying this Court's *Mayo* and predecessor precedent in finding largely that the "markedly different" properties of the isolated DNA made the isolated DNA a man-made invention deserving of a patent. The case before this Court is not a *Chakrabarty*-like bacterium involving human engineering at the core of the claim. Rather, the case before this Court is about human engineering the edges of naturally occurring DNA in a particular way as discussed in greater detail below. The Federal Circuit's decision in *Ass'n for Molecular Pathology* fails to explain how human engineering the edges of naturally occurring DNA amounts to more than extra-solution activity preemptive of a fundamental principle; thereby amounting to an invention deserving of a patent.

As the Court has repeatedly pointed out in *Mayo* and its predecessor cases, even a product decidedly "new" and "useful" may nonetheless fail § 101 if the composition preempts the fundamental principle itself. For as this Court held in *Mayo*, if a new and useful product "too broadly preempt[s] the use of a natural law," it is not an invention created by man and so it is not patent eligible subject matter. As the Court noted in *Funk Bros.* "there is no way in which we could call it such [an invention] unless we borrowed invention from the discovery of the natural principle itself." 333 U.S. 133.

Through the prism of "preemption" that the Court has provided in *Mayo* and predecessor decisions, the question of whether isolated DNA is patent eligible subject matter can be finally answered.

IV. The "engineering at the edges of DNA" for "packaging" of natural DNA does not create the quality in the recited isolated DNA useful for diagnostic targeting which is the work of nature. Those qualities of DNA are not an "invention" or "discovery" under this Court's *Mayo* and *Funk Bros.* decisions for patents cannot issue for the discovery of this phenomenon of nature

Myriad ascertained that two "isolated" human genes, *BRCA1* and *BRCA2* (collectively, "*BRCA1/2*" or "*BRCA*"), and certain alterations, or mutations, in these genes are associated with a predisposition to breast and ovarian cancers. *Ass'n for Molecular Pathology*, *supra* at 1309. Myriad then isolated these genes for use in providing BRCA diagnostic testing services to women. *Id.*, at 1314.

Representative composition claims before this Court include claims 1, 2, and 5 of the '282 patent:

> 1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.
>
> 2. The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1.
>
> 5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.

Id., at 1309.

The Federal Circuit construed the claims in several places as follows:

> Isolated DNA, in contrast, is a free-standing portion of a larger, natural DNA molecule. Isolated DNA has been cleaved (*i.e.*, had covalent bonds in its backbone chemically severed) or synthesized to consist of just a fraction of a naturally occurring DNA molecule. *Id.*, at 1328.

As discussed in detail in the Section V of this brief, to be sure, some of the claims may require more than simply the isolation of natural DNA from its natural habitat and those claims require further analysis. But claims that differ from naturally occurring DNA only because they are isolated falls squarely within the ambit of the sole issue before this Court which is "Are human genes patentable?"

The Federal Circuit relied on the foregoing construction of the claims (*i.e.*, that isolated DNA has a "cleaved" structure) in holding the isolated DNA to be patent eligible subject matter. *Id.*, at 1328, 1329. In short, the difference between isolated DNA and natural DNA resides largely from the "cleaved" structure (*i.e.*, broken covalent bonds in the backbone, removal of genetic material, etc.). *Ass'n for Molecular Pathology*, *supra* at 1328.

To determine whether 35 U.S.C. § 101 is satisfied, it is necessary to consider the claim as a whole. *Diehr*, 450 U.S. at 188. The claims as a whole recite a "DNA" component and a "cleaved" component that together form the recited cleaved composition known as isolated DNA.

DNA is a product of nature regardless of amount. DNA is DNA whether it includes its entire make-up or a fraction thereof as recited in the asserted claims. As a product of nature, DNA alone is not patent eligible subject matter. Hence, if there is to be invention from a discovery involving DNA, it must come from the application of the law of nature to a new and useful end. *Mayo*, *supra* at 1294 and *Funk Bros.*, *supra* at 131. See also *Telephone Cases*, 126 U.S. 1, 532-533 (1888); *De Forest Radio Co. v. General Electric Co.*, 283 U.S. 664, 684-685 (1931); *Mackay Radio & Tel. Co. v. Radio Corp.*, 306 U.S. 86, 94 (1939).

The Federal Circuit noted that the difference between isolated DNA and natural DNA resides largely in the "cleaved" structure (*i.e.*, broken covalent bonds in the backbone, removal of genetic material, etc.). In other words, the application involving DNA recited in the isolated DNA claims largely amounts to a way in which to chemically package certain fractions of DNA. It is human engineering done at the edges of the DNA in order to contain the naturally occurring DNA in a tidy package. More specifically, the broken covalent bond structure in the backbone, the removal of genetic materials, etc., largely provides a "chemical package" in order to contain the piece of naturally occurring DNA for use in diagnostic detection purposes. In other words, natural DNA resides in the genetic mass resulting from the human engineered detection delivery package. The human engineered package makes the natural DNA which is contained therein useful for diagnostic detection purposes.

While the "cleaved" packaging makes the isolated DNA a composition that is "new" as the Federal Circuit has held, the question of "invention" or "discovery" under § 101 turns on whether that new packaging of DNA can be called an invention deserving of a patent under § 101. Under the Court's *Mayo* and *Funk Bros.* precedent, isolated DNA falls short of invention within the meaning of § 101.

The packaging of DNA into an isolated DNA does not create the quality in the recited DNA useful for diagnostic targeting. The diagnostic targeting quality of the isolated DNA is the work of nature. Those qualities of DNA are not patentable. For patents cannot issue for the discovery of this phenomenon of nature. *Mayo*, *supra* at 1294; see also *Funk Bros.*, 333 U.S. 131.

The qualities of DNA for use in diagnostic targeting, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men. *Mayo*, *supra* at 1294. See also *Funk Bros.*, 333 U.S. 131. The qualities of DNA for use in diagnostic targeting are manifestations of laws of nature, free to all men and reserved exclusively to none. *Mayo*, *supra* at 1294. See also *Funk Bros.*, 333 U.S. 131. As the Court decisions in *Mayo* and *Funk Bros.* make clear, he who discovers a before unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes. *Mayo, supra* at 1294 and *Funk Bros., supra* at 131.

The application of the "cleaved" packaging to the problem of packaging natural DNA for diagnostic detection purposes is an important commercial advance. But once nature's secret of the diagnostic detection quality of human genes *BRCA1* and *BRCA2* was discovered, the state of the art made the production of a chemically packaged DNA SEQ of those human genes by "cleaving" for use in diagnostic detection a simple step. However ingenious the discovery of the natural principle of correlating human genes *BRCA1* and *BRCA2* with a predisposition to breast and ovarian cancers may be, the application of that discovery through isolation of the relevant DNA is hardly more than an advance in the "chemical packaging" of the DNA. It is human engineering of the DNA at the edges. The DNA contained in the "cleaved" package targets the same DNA SEQ which the natural DNA SEQ is disposed to target. No isolated DNA acquires a different use. The isolation of DNA produces no new DNA, no change in the DNA, and no enlargement of the range of their utility. The DNA has the same effect in isolated form as it always had. The DNA in isolated DNA performs in its natural way. The isolated DNA does not improve in any way natural functioning of the DNA. The isolated DNA serves the ends nature originally provided, and acts independently of any effort of the patentee.

The identification of the recited SEQ as an effective marker of DNA sites is an important discovery;

allowing the medical community to know which portion of DNA to isolate for use in the diagnostic detection of *BRCA1* and *BRCA2* and mutations thereof. But the correlation that is derived between *BRCA1* and *BRCA2* and predisposition to breast and ovarian cancer is a correlation existing in nature. It is not a correlation created by human ingenuity and hence is not patentable matter. *Mayo*, *supra* at 1294.

The "cleaved" packaging resulting from "engineering the edges" of the natural DNA that is done to create the recited isolated DNA SEQ does bring significant advantages to the DNA SEQ isolated when compared to the form taken by the DNA SEQ as it exists in nature. The packaging provides an effective vehicle for use in diagnostic targeting. The packaging prepares the DNA SEQ for use in diagnostic targeting. But a product must be more than new and useful to be patented; it must also satisfy the requirements of invention or discovery. *Mayo*, *supra* at 1294. See also *Funk Bros.*, 333 U.S. 131.

The "cleaved" packaging in *Ass'n for Molecular Pathology* is not unlike the general purpose computer in *Benson* and *Flook* and the technological field limitation in *Flook*. Neither are central to the claim. Each are insignificant extra-solution activity. In *Benson*, "once that algorithm [wa]s assumed to be within the prior art, the application, considered as a whole, contain[ed] no patentable invention." *Flook*, at 594. In *Ass'n for Molecular Pathology*, once the *BRCA1* and *BRCA2* DNA correlation was assumed to be in the prior art, the "application" of cleaving of the covalent bonds, that is to say, the engineering of the edges of the naturally occurring DNA SEQ to put the naturally occurring DNA SEQ into the recited isolated packages for diagnostic targeting purposes, considered as a whole, contained no patentable invention.

The biotech community knows that you can place a selected piece of a naturally occurring DNA SEQ that you want to use for diagnostic targeting into a cleaved package. The biotech community knows that you can engineer the edges of the selected DNA SEQ as it exists in the body, by cleaving the covalent bonds, in order to provide a vehicle for use in determining a correlation existing in nature useful in diagnosing a condition. The biotech community knows how to engineer the edges of the DNA to do this. While it may be the case that there may be other ways to test for predisposition without using isolated DNA, that doesn't change the fact that isolating DNA for use in detecting a predisposition is a standard way that the biotech industry uses to do this. See *Ass'n for Molecular Pathology*, *supra* at 1333. ("[I]t is estimated that the PTO has issued 2,645 patents claiming "isolated DNA" over the past twenty-nine years.") Beyond isolating the natural DNA SEQ, the human engineered package does largely no more than to hold that naturally occurring DNA SEQ and make it useful for determining the correlation useful for detecting a biological condition all of which occurs by the handiwork of nature.

Once the correlation of the *BRCA1* and *BRCA2* DNA SEQ to a predisposition to breast and ovarian cancers was known, the packaging of that DNA SEQ into a cleaved package by engineering the edges of the DNA SEQ was a matter of known practice; an insignificant extra-solution activity. Hence, the application of cleaved packaging to isolate the natural DNA SEQ, considered as a whole, contains no patentable invention. Absent the known packaging, the *BRCA1* and *BRCA2* DNA SEQ is all that remains and that is not patent eligible matter.

There seems to be no way in which the Court could call isolated DNA as being an "invention" or "discovery" under § 101 unless the Court borrowed invention from the discovery of the natural principle itself. In other words, there is no invention in isolated DNA unless the discovery that the correlation of the *BRCA1* and *BRCA2* DNA SEQ to a predisposition to breast and ovarian cancers is invention. But under the preemption doctrine of *Mayo* and *Funk Bros.*, the Court cannot hold the isolated DNA to be patent eligible subject matter without allowing a patent to issue on one of the fundamental principles of nature, DNA itself.

All that remains, therefore, in the isolated DNA as claimed are advantages provided by the "cleaved" package made possible by "engineering the edges" of the naturally occurring DNA SEQ by cleaving of the covalent bonds to form the isolated DNA itself; an insignificant extra-solution activity. That should not be enough.

Since the isolated DNA product claims do not disclose an invention or discovery within the meaning of § 101 of the patent statutes, the isolated DNA patent claims should be held invalid. The Federal Circuit holding to the contrary should be reversed.

V. The claims which are directed to isolated sequences that are identical to naturally occurring gene sequences fall squarely within the discussion of Section IV above and are not human invention. However, the judgment of the Federal Circuit as to isolated cDNA product claims should be vacated and the case should be remanded to the United States Court of Appeals for the Federal Circuit for further consideration of whether the packaging of the DNA SEQ into cDNA molecules is an insignificant extra-solution activity or "human invention" deserving of a patent

As discussed in detail in Section IV of this brief, to be sure, some of the claims may require more than simply the isolation of natural DNA from its natural habitat and those claims require further analysis.

As Judge Moore noted in her concurring opinion:

> The isolated DNA claims of the patents in suit fall into two categories. The first category of claims is directed to isolated sequences that are identical to naturally occurring gene sequences. These include claims encompassing both the isolated full length gene

> sequence (e.g. claim 1 of '282 patent), which are thousands of nucleotides, and claims to shorter isolated DNA strands, with as few as fifteen nucleotides, whose nucleotide sequence is found on the chromosome (e.g. claim 5 of '282 patent). The second category of claims is directed to isolated DNA sequences that are different from the naturally occurring gene sequences. These include claims to isolated cDNA molecules (e.g. claim 2 of the '282 patent), which differ from the natural gene sequence in that the introns are removed, and are the opposite (complementary) sequence of the naturally occurring RNA.

Ass'n for Molecular Pathology, *supra*, concurring at 1340.

The first category of claims which are directed to isolated sequences that are identical to naturally occurring gene sequences falls squarely within the discussion of Section IV above. All that remains in those isolated DNA as claimed are advantages provided by the "cleaved" package made possible by "engineering the edges" of the naturally occurring DNA SEQ by cleaving of the covalent bonds to form the isolated DNA itself; an insignificant extra-solution activity. That should not be enough. Since those isolated DNA product claims do not disclose an invention or discovery within the meaning of § 101 of the patent statutes, those isolated DNA patent claims should be held invalid. The Federal Circuit holding to the contrary should be reversed.

The second category of claims, which are isolated cDNA molecules (e.g. claim 2 of the '282 patent) (*id.*, at 1340, 1341), differ from the natural gene sequence in that the introns are removed, and are the opposite (complementary) sequence of the naturally occurring RNA. *Id.* The judgment of the Federal Circuit as to those isolated DNA product claims should be vacated and the case should be remanded to the United States Court of Appeals for the Federal Circuit for further consideration in light of the decision of this Court in this isolated DNA case now before it. In particular, the Federal Circuit should consider whether the packaging of the DNA SEQ into cDNA molecules is an insignificant extra-solution activity or "human invention" deserving of a patent. It would be improvident to decide this difficult question without fully briefing this question.

VI. The Court should clarify that "preemption" in isolated DNA arises not from isolated DNA being not "new"; rather that the isolated DNA is not an "invention" or "discovery" entitled to a patent under § 101

There seems to be a great deal of confusion in the patent community about preemption and in particular which requirement in § 101 invokes the preemption doctrine. The case law suggests that preemption may be triggered by either or both "new" and "invention" requirements in § 101. For example, claims directed to "pure DNA" would appear to fail because "pure DNA" is not "new." On the other hand, the "isolated DNA" claims before this Court that fail would appear to do so because albeit "new," those "isolated DNA" claims are not "inventive."

The Court's decision in the isolated DNA case now before it is believed will provide much valuable guidance on this important point.

◆

CONCLUSION

The judgment of the court of appeals directed to isolated sequences that are identical to naturally occurring gene sequences reversing the district court's ruling under 35 U.S.C. § 101 should be reversed. The judgment of the court of appeals directed to isolated cDNA product claims should be vacated and the case should be remanded to the United States Court of Appeals for the Federal Circuit for further consideration of whether the packaging of the DNA SEQ into cDNA molecules is an insignificant extra-solution activity or "human invention" deserving of a patent.

Respectfully submitted,

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January 28, 2013

AMICUS
CURIAE
BRIEF

RECORD
AND
BRIEFS

Supreme Court, U.S.
FILED

JAN 3 1 2013

OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR
PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES
COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF PROFESSOR EILEEN M. KANE AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

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INTEREST OF *AMICUS CURIAE*

Professor Eileen M. Kane teaches patent law and intellectual property law in the United States, and her legal scholarship has focused on the intersection of patent law and the life sciences, with particular attention to the field of genetics.[1] Professor Kane has a Ph.D. in molecular biology and is a registered attorney before the United States Patent and Trademark Office. She has no financial interest in the above referenced case. This brief is submitted because of the continuing importance of striking a balance between the patent system and the public domain.

SUMMARY OF THE ARGUMENT

DNA is a unique molecule in the life sciences because it is the chemical repository of inheritance, written in the language of the genetic code. Genes are nature's formulas of the genetic code. Modern genetic science has been defined by the imperative to discover the full set of genes in the human genome.

Are human genes patentable? Not everything can be patented. This Court's careful application of the patentable subject matter doctrine of 35 U.S.C. § 101 has provided guardianship for the "storehouse of knowledge" (*Funk*

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[1] Petitioners' letter of consent to file amicus briefs is on file with the Court; Respondents' emailed consent is attached to this brief. This brief was not authored in whole or in part by counsel for any party and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than amicus curiae made a monetary contribution to its preparation or submission.

Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 130 (1948)) and the "basic tools" (*Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)) that comprise the intellectual inputs for patentable inventions. The Court has been quite clear that the "laws of nature, natural phenomena, and abstract ideas" are not patentable. *Diamond v. Diehr*, 450 U.S. 175, 185 (1981). The underlying rationale for these exclusions is that scientific advances originate from widely available basic knowledge, and therefore, patenting the intellectual substrates of a field has an adverse effect on its progress. In *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), this Court recently confirmed the requirement for an "inventive concept" in order to establish patentable subject matter that is derived from the natural world.

Genes are not invented. This Court's jurisprudence provides the basis for concluding that patent claims on human genes violate long-standing prohibitions against patenting laws of nature and products of nature. This brief presents two theories of patent ineligibility, grounded in the Court's precedent, that disqualify genes as patentable subject matter: specific and general. First, the gene is a DNA molecule with a specific patent ineligibility that results from its unique property as the repository of the genetic code. The genes are the naturally occurring embodiments of the genetic code. The patenting of genes preempts the use of the genetic code and therefore preempts a law of nature. Second, the gene is a DNA molecule that is generally ineligible for patenting in view of the product of nature doctrine, which requires an inventive conversion of a natural product to secure patent rights. The isolated gene of the challenged patent claims retains natural structure in order to execute natural function. It is a product of nature, and as such, cannot be patented.

In determining patentable subject matter, *Mayo* requires the Court to measure any inventive contribution against the foreclosure of future innovation. That calculation leads to the conclusion that gene patenting exhibits an acute asymmetry: the absence of any inventive contribution is coupled with a damaging effect on the ability of scientists and medical practitioners to freely utilize the most basic discoveries of genetic science, with adverse consequences for the development of innovative advances in genetic medicine. Genes do not constitute patentable subject matter, and the patent claims should be invalidated.

ARGUMENT

I. The Exclusion of Laws and Products of Nature from Patenting Is Necessary to Generate Inventive Achievement

The boundaries of patentable subject matter are critical to a functioning patent system that encourages inventive achievement. Just last year, in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), this Court revisited the doctrine of patentable subject matter as applied to the life sciences. Mayo involved patent claims to methods for determining optimal pharmaceutical dosing by using the correlations between metabolite levels and drug toxicity, which the Court characterized as a "law of nature." *Id.* at 1296. The Court unanimously concluded that the patent claims lacked any inventive contribution beyond merely reciting the correlations; it stated that the steps recited in the method claim "add nothing of significance to the natural laws themselves," and that the claims were thus invalid under 35 U.S.C. § 101. *Id.* at 1302.

Mayo made several general points regarding the necessity and rationale for the use of the patentable subject matter doctrine of 35 U.S.C. § 101. First, the Court reaffirmed the necessity for performing an eligibility analysis in the examination of a proposed invention for compliance with the patent statute. The Court explicitly declined an invitation to avoid patentable subject matter questions by substituting the other doctrinal requirements for patentability (*e.g.*, utility under 35 U.S.C. § 101, novelty under 35 U.S.C. § 102, nonobviousness under 35 U.S.C. § 103, and the disclosure doctrines of 35 U.S.C. § 112), noting that "to shift the patent eligibility inquiry entirely to these later sections risks creating significantly greater legal uncertainty." *Id.* at 1304.

Second, *Mayo* reaffirmed the complexity of the patentable subject matter inquiry, noting that the reach of 35 U.S.C. § 101 is not without limit: "The Court has long held that this provision contains an important implicit exception. '[L]aws of nature, natural phenomena, and abstract ideas' are not patentable." *Id.* at 1293 (quoting *Diamond v. Diehr*, 450 U.S. 175, 185 (1981)). The Court defined the policing of patentable subject matter by these categorical exclusions as a necessary predicate to maintaining a common stock of scientific knowledge in the public domain. "[T]he cases have endorsed a bright-line prohibition against patenting laws of nature, mathematical formulas and the like, which serves as a somewhat more easily administered proxy for the underlying 'building block' concern." *Id.* at 1303. Several years earlier, this Court had also reiterated the continuing relevance of these exclusions: "The concepts covered by these exceptions are 'part of the storehouse of knowledge of all men ... free to all men and reserved exclusively to none.'" *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010) (quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)).

These modern statements from *Mayo* and *Bilski* echo the Court's observation from 40 years ago: "Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972). The sum of these pronouncements from the Court signals that it regards the patentable subject matter doctrine as providing a guardianship of the "basic tools," the "building blocks" and the "storehouse of knowledge" of science – all of which are to be protected from private appropriation when 35 U.S.C. § 101 is applied with the precision demanded by this Court's jurisprudence.

The challenged composition of matter claims recite the naturally occurring wild-type genes or naturally occurring mutated genes that correspond to the native human BRCA1 and BRCA2 genes, although described in the claim language of "isolated DNA" (Claims 1, 2, and 7 of U.S. Patent No. 5,747,282, Claims 1, 6, and 7 of U.S. Patent No. 5,837,492 and Claim 1 of U.S. Patent No. 5,693,473). Patent claims that comprise fragments of the BRCA1 gene can also operate to cover the use of the full-length gene (Claims 5 and 6 of U.S. Patent No. 5,747,282); as a result, their validity is subject to the same eligibility analysis.

Although the challenged patent claims to "isolated DNA" can be classified as compositions of matter with respect to the formal categories of inclusion detailed in 35 U.S.C. § 101, the analysis does not end there. Patent claims must not capture the basic knowledge tools that are essential for maintaining the vibrant intellectual climate of a technological field. "Patent law seeks to avoid the dangers of overprotection just as surely as it seeks to avoid the diminished incentive to invent that underprotection can threaten. One way in which patent law seeks to sail between these opposing and risky shoals is through rules that bring certain types of invention and discovery within the scope of patentability while excluding others." *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 127 (2006) (Breyer, J., dissenting from the dismissal of the writ of certiorari as improvidently granted). The application of the law of nature doctrine and the product of nature doctrine to the isolated genes of the challenged patent claims is necessary to discern whether such claims impermissibly appropriate subject matter that belongs in the public domain. Detailed examination reveals that isolated genes remain products of nature, and their patenting preempts a law of nature. As such, they fail to meet this Court's standards for patentable subject matter.

II. The Gene Has a Specific Patent Ineligibility Because Its Patenting Preempts a Law of Nature

A. The Genes are the Natural Embodiments of the Genetic Code, Which Is a Law of Nature

Unraveling the biochemical infrastructure of inheritance revealed an underlying law of nature that explained the unique structure of DNA. "Only when the structure of DNA was discovered in the early 1950's did it become clear how the hereditary information in cells is encoded in DNA's sequence of nucleotides." Bruce Alberts et al., MOLECULAR BIOLOGY OF THE CELL 299, 4th edition (2002). The molecular design of DNA was then understood to convey an informational code that accounted for its ability to function as the chemical repository of inheritance. A genetic code was discovered and deciphered, revealing a set of equivalences that link a specific DNA nucleotide sequence to a specific protein sequence. *Id.* at 336. The gene functions as a template according to the genetic code. "The genetic code is not the message itself but the 'dictionary' used by the cell to translate from the four-letter language of nucleic acid to the 20-letter language of protein." Frances Crick, *The Genetic Code III*, 215 Scientific American 55 (1966). The correlation between DNA and protein is central to the gene patent claims at issue. Claim 1 of U.S. Patent No. 5,747,282 is a representative illustration of reliance on the genetic code when it simply claims "an isolated DNA coding for a BRCA1 polypeptide." "[T]he relation itself exists in principle apart from any human action." *Mayo*, 132 S. Ct. at 1297.

The leading historian of the genetic code noted that the universality of the genetic code across the biological world was especially significant because "it would elevate the genetic code to the pedestal of universal laws of nature, a privilege usually reserved for the Olympian reaches of physics." Lily E. Kay, WHO WROTE THE BOOK OF LIFE?: A HISTORY OF THE GENETIC CODE 276 (2000). The realization that the genetic code functioned as a natural law in the biological sciences led scientists to refer to the DNA-protein relation as the "central dogma" of molecular biology. Alberts et al., MOLECULAR BIOLOGY OF THE CELL, at 301.

The genetic code, therefore, is equivalent in status to the laws of physics previously recognized as unpatentable laws of nature in this Court's patentable subject matter jurisprudence. "The laws of nature, physical phenomena, and abstract ideas have been held not patentable. Thus, a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity. Such discoveries are 'manifestations of....nature, free to all men and reserved exclusively to none.'" *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) (quoting *Funk Bros.*, 333 U.S. at 130). This recitation of unpatentable scientific laws by the Court provides a firm basis for concluding that the discoveries of scientific equivalences, whether the metabolite-toxicity relationship in *Mayo* or the genetic code in this case, cannot be patentable subject matter; in fact, these are precisely the kinds of intellectual achievements that must be segregated from the patent system so that they can be used freely by all. The designation of the genetic code as a law of nature has implications for the patenting of its natural embodiments, which are the genes.

Genes are nature's exemplars of the genetic code – as such, they embody the law of nature. The conversion of the genetic code into a human organism is accomplished by the set of formulas that are individually encapsulated as the genes. The gene, while formally described as a chemical compound, is functionally explained as a template. The dynamic gene operates by the laws of the genetic code. Activation of a gene initiates a sequence of metabolic events that unfold to accomplish the ultimate objective of generating a protein from a gene, a process generally known as gene expression. Extensive scientific efforts have been expended to locate and characterize the genes and to sequence the full human genome, finally culminating in the efforts of the Human Genome Project. International Human Genome Sequencing Consortium, *Finishing the Euchromatic Sequence of the Human Genome*, 431 Nature 931 (2004). The human genes are the natural formulas of the genetic code that are embedded in the human genome.

The use of the genetic code in genetic medicine is accomplished by research into the behavior of the genes, which dictate the structure and function of the human organism. While the science is novel and paradigm-shifting, its impact is explained by its use of the naturally occurring molecules, the genes, to arrive at a precise and individualized account of an individual's genetic and biochemical identity. "[T]he ultimate consequences of the integration of genomics into medical research and medical practice are likely to be revolutionary." Alan F. Guttmacher and Francis S. Collins, *Realizing the Promise of Genomics in Biomedical Research*, 294 J. Am. Med. Ass'n 1399 (2005). The use of the genes is critical because these molecules carry the natural templates of the human organism. Thus, scientists must draw on the fundamental and uninvented principles of genetics to in order to develop practical applications for use in genetic medicine.

Despite the technical work that underlies the identification and sequencing of the natural genes, there can be no dispute that such efforts do no more than reveal a natural blueprint. "The genome sequence is a discovery, not an invention." John Sulston & Georgina Ferry, THE COMMON THREAD: A STORY OF SCIENCE, POLITICS, ETHICS, AND THE HUMAN GENOME 266 (2002). Accordingly, because the genes are the natural embodiments of the genetic code, the eligibility analysis of these molecules necessarily implicates the effect of patenting on the availability of this underlying law of nature. More precisely for patent law, this question is generally framed as investigating whether a law of nature is preempted by the grant of a patent claim, an outcome that conflicts with this Court's precedents. "The rule that the discovery of a law of nature cannot be patented rests, not on the notion that natural phenomena are not processes, but rather on the more fundamental understanding that they are not the kind of discoveries that the statute was enacted to protect." *Parker v. Flook*, 437 U.S. 583, 593 (1978).

B. The Patenting of Genes Preempts the Genetic Code, and Is Invalid According to the Court's Prohibition Against Patenting Laws of Nature

Although the Court has repeatedly stated that laws of nature, natural phenomena and abstract ideas are not patentable subject matter, the Court has been alert to possible preemption of the underlying idea through patenting practices. The Court recently elaborated on the underlying rationale for the law of nature exception when it cautioned against "the kind of risk that underlies the law of nature exception, namely the risk that a patent on the law would significantly impede future innovation." *Mayo*, 132 S. Ct. at 1304. The preemption analysis from the Court's jurisprudence provides the analytic tool for avoiding such risk. The claimed mathematical process in *Benson* provided such an example: "The mathematical formula involved here has no substantial practical application except in connection with a digital computer, which means that if the judgment below is affirmed, the patent would wholly pre-empt the mathematical formula and in practical effect would be a patent on the algorithm itself." *Benson*, 409 U.S. at 71-72 (1972).

Preemption of fundamental subject matter has been the focus of the two most recent patentable subject matter cases from this Court. Just last year, the Court defined a persistent concern from its jurisprudence when it noted that its cases "warn us against upholding patents that claim processes that too broadly preempt the use of a natural law." *Mayo*, 132 S. Ct. at 1294. Applying that warning to its analysis of the medical treatment claims in *Mayo*, the Court found preemption of an uninvented correlation between drug metabolism and toxicity when it reasoned that "upholding the patents would risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries." *Id.* In 2010, the Court employed a preemption analysis in concluding that the patenting of a method for hedging the risk of price changes had too broad an occlusive effect. "Allowing petitioners to patent risk hedging would preempt use of this approach in all fields, and would effectively grant a monopoly over an abstract idea." *Bilski*, 130 S. Ct. at 3231 (2010).

The preemption analysis can be applied to the isolated DNA claims at issue, because the claimed genes embody the most fundamental law of nature from biology, the genetic code. The issued patents in this case unambiguously document the natural identity of the claimed BRCA1 gene: "The nucleic acids of the present invention will possess a sequence which is either derived from, or substantially similar to a *natural* BRCA1-encoding gene or one having substantial homology with a *natural* BRCA1-encoding gene or a portion thereof." U.S. Patent No. 5,747,282, column 19, lines 44-48 (italics added). The natural identity of the claimed BRCA2 gene is similarly described: "The nucleic acids of the present invention will possess a sequence which is either derived from, or substantially similar to a *natural* BRCA2-encoding gene or one having substantial homology with a *natural* BRCA2-encoding gene or a portion thereof." U.S. Patent No. 5,837,492, column 18, lines 29-33 (italics added). Although the patent claims are formally directed to "isolated DNA," the actual DNA sequence is the sequence of the "natural" wild-type or mutated gene, as the patents describe.

The patents claim to the isolated DNA at issue cover natural and uninvented expressions of the genetic code, and have preemptive effect. The genetic code, which is an unpatentable law of nature, does not effectively reside in the public domain if private rights are held in DNA gene sequences, so that the use of the nature's expressions of the genetic code - the genes - are controlled through patent rights. The patenting of genes, therefore, results in effective preemption of the genetic code, an outcome that conflicts with the Court's dictate that the laws of nature should remain in the public domain, free for all to use. Eileen M. Kane, *Splitting the Gene: DNA Patents and the Genetic Code*, 71 Tenn. L. Rev. 707, 753 (2004).

The question presented in this case offers the Court an opportunity to resolve patent eligibility for the entire class of human genes, which comprise the human genome. A proper patentable subject matter analysis of one gene patent claim will resolve the patent eligibility for the class of molecules, because the relevant analysis is generic and not gene-specific. The human genome can be understood as the compilation of nature's formulas for the construction of the human organism. Each and every gene patent has preemptive effect because it withdraws the use of one of nature's genetic formulas; an outcome that allows "a patent to issue on one of the ancient secrets of nature now disclosed." *Funk Bros.*, 333 U.S. at 131.

The merger doctrine from copyright law supplies a relevant theoretical framework for understanding preemption in the context of genetic science. According to this doctrine, if an uncopyrightable idea has a set of finite expressions, then property rights in the expressions are tantamount to ownership of the underlying idea; effectively, the idea and the expressions merge. *Baker v. Selden*, 101 U.S. 99 (1879). The genes are nature's finite set of embodiments of the genetic code. Moreover, they are not modular or redundant - each embodiment is unique. The grant of private rights to the embodiments of the genetic code results in an effective grant of rights to the code itself. At the level of the human genome, the patenting of genes can be viewed as a merger problem writ large - if the embodiments of the underlying law of nature are subject to private appropriation through patent rights, then the underlying law of nature has itself entered the private domain. Kane, *supra*, at 754. Such an outcome does not comport with the *Mayo* requirement that "to transform an unpatentable law of nature into a patent eligible *application* of such a law, one must do more than simply state the law of nature while adding the words "apply it." *Mayo*, 132 S. Ct. at 1294 (italics in original). Because the correlation between a DNA sequence and its cognate protein is a law of nature, and this correlation is central to the patent claims at issue, the claims are fatally analogous to the patent claims invalidated in *Mayo*, which failed to demonstrate "more than a drafting effort designed to monopolize the law of nature itself." *Id.* at 1297. "The question before us is whether the claims do significantly more than simply describe these natural relations. To put the matter more precisely, do the patent claims add *enough* to their statements of the correlations to allow the processes they describe to qualify as patent eligible processes that *apply* natural laws?" *Id.* (italics in original). In this case, patent claims to isolated genes simply "inform a relevant audience about certain laws of nature." *Id.* at 1298. They do no more.

The Federal Circuit did not consider a law of nature analysis to be relevant to its analysis of composition of matter claims. "[P]ermitting patents on isolated genes does not preempt a law of nature." *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 689 F.3d 1303, 1331 (Fed. Cir. 2012). The court then acknowledged that "limited preemption" could be tolerated, but it then mischaracterized the concept of preemption ("a limited preemption is inherent in every patent). *Id.* However, preemption refers, in this Court's jurisprudence, to instances where patenting can block access to certain unpatentable forms of subject matter. That definition of preemption is independent of technological field or claim format, and it does not support a quantification of preemption. In fact, *Mayo* explicitly declined to "draw distinctions among laws of nature." *Mayo*, 132 S. Ct. at 1303. The Federal Circuit thus failed to apply all relevant analytic tools from this Court's jurisprudence in its eligibility analysis of isolated genes, and it did not fully consider the complexity of the DNA molecule. The duality of DNA as both chemical and template requires a bifurcated legal analysis that draws on both process-based and product-based doctrines of eligibility developed in patentable subject matter jurisprudence to derive analytic principles suitable for the eligibility analysis of a gene. Contrary to the court's assertion that a "categorical rule" is created by a DNA-specific eligibility analysis, the law of nature analysis of patented genes is necessitated by the multidimensional nature of the gene, and it is a logical application of well-established eligibility criteria from this Court. Gene patenting results in the preemption of a law of nature, the genetic code, and, consequently, the isolated genes do not constitute patentable subject matter.

III. The Gene Has a General Patent Ineligibility As a Product of Nature

A. The Isolated Gene Retains a Natural Structure Dictated by Natural Function, and is Not Markedly Different from the Cellular Gene

When considering whether a genetically engineered bacterium became an invented product, the Court noted that the patentable subject matter inquiry must distinguish "between products of nature, whether living or not, and human-made inventions." *Chakrabarty*, 447 U.S. at 313. The distinction between a product of nature and an invented product was further defined by the Court when it recognized that an inventive conversion of a natural product would require the demonstration of "markedly different characteristics" in a claimed product. *Id.* at 310. The Court recognized that patent eligibility could be satisfied by a "product of human ingenuity" "having a distinctive name, character [and] use." *Id.* at 309-10.

In order to apply this Court's standard to the present case, the comparison of the "isolated DNA" in the composition of matter claims on wild-type and mutant genes to the naturally occurring genes has two separate inquiries. Formally, these are the questions of structure and function. Is the isolated DNA structurally identical to the native gene? Does the isolated DNA function in the same manner as the native gene? However, these questions converge for DNA. The structure of the isolated DNA of the patent claims is not chosen, and certainly not invented, but required - because it will provide the natural function of the gene.

Structure and function converge in the patent claims at issue. Claim 1 of U.S. Patent No. 5,747,282 is representative of this convergence when it claims "an isolated DNA coding for a BRCA1 polypeptide" – claiming a molecule with a structure that will allow it to execute its normal function, which is to encode the BRCA1 protein. The patent claim simply "reports" that a particular DNA sequence encodes the amino acid sequence that constitutes a natural protein.

The isolated DNA of the patent claims is a product of nature's design. While Claim 1 of U.S. Patent No. 5,747,282 reports a DNA sequence defined by "coding," other challenged claims report DNA coding sequences written in complementary DNA (cDNA) format (*e.g.*, Claim 2 of U.S. Patent No. 5,747,282). A purified gene is often claimed as an isolated cDNA - the abbreviated, message-bearing form of the gene. Alberts et al., MOLECULAR BIOLOGY OF THE CELL, at 503. The cDNA molecule is produced by routine, conventional laboratory protocols. Jonathan Pevsner, BIOINFORMATICS AND FUNCTIONAL GENOMICS 302, 2nd edition (2009). The goal of recovering the gene sequence as a cDNA is to preserve the "natural" informational content of the molecule so that it is identical to the native gene. The patents in this case document the functional identity - and therefore structural identity - of the isolated BRCA1 DNA to native genes, describing "a sequence which is either derived from, or substantially similar to a *natural* BRCA1-encoding gene," U.S. Patent No. 5,747,282, column 19, lines 45-46 (italics added); the identity of isolated BRCA2 DNA to the native genes is noted by "a sequence which is either derived from, or substantially similar to a *natural* BRCA2-encoding gene," U.S. Patent No. 5,837,492, column 18, lines 30-31 (italics added). Those statements simply report that structure will implement function for the isolated DNA molecules, and that the function is nothing more than the mechanical reproduction of nature's blueprint. This conclusion applies to all challenged patent claims – whether primarily defined by function ("coding for") or primarily defined by structure (cDNA). All such claims have identical effect, which is to claim patent rights on a naturally occurring BRCA1 or BRCA2 gene. In fact, any deviation from the natural DNA sequence would compromise the use of the isolated DNA as the functional equivalent of the cellular gene, as the patented molecules provide the foundation for Myriad's BRCA1 and BRCA2 genetic tests. The mimicry of the native gene undermines any assertion that an inventive alteration has occurred.

In *Funk Bros.*, this Court considered whether the repackaging of natural bacterial strains in a mixed inoculant created a patent-eligible product. The Court concluded that neither structure or function were altered in the claimed bacterial product: "The bacteria perform in their natural way. Their use in combination does not improve in any way their natural functioning.

They serve the ends nature originally provided and act quite independently of any effort of the patentee." *Funk Bros.*, 333 U.S. at 131. By analogy, the isolated genes retain a structure that allows their natural function to be maintained, and "serve the ends nature originally provided." *Id.* They are products of nature, and cannot be patented.

B. There is No Inventive Conversion of the Isolated Gene, and it Remains an Unpatentable Product of Nature

The tests derived from this Court's jurisprudence for identifying an unpatentable product of nature focus on difference. The "markedly different characteristics" required by *Chakrabarty* are further amplified with reference to "having a distinctive name, character [and] use." *Chakrabarty*, 447 U.S. at 309-310. *Funk Bros.* examined the properties of the claimed bacterial inoculant to determine if they reflected any inventive input. "The qualities of these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men. They are manifestations of laws of nature, free to all men and reserved exclusively to none." *Funk Bros.*, 333 U.S. at 130. The Court stated that the inventor had simply made a "discovery of some of the handiwork of nature." *Id.* at 131. No human intervention accounted for the properties exhibited by the bacteria, and the Court did not conflate discovery with invention.

In *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1 (1931), directed to a claimed invention of a chemically-treated orange, the Court decided that the addition of borax to the rind of an orange to increase its longevity did not confer a patentable distinction, when compared to an unadulterated orange, to create an article of manufacture, stating that "[a]ddition of [the] borax to the rind of [the] natural fruit does not produce from the raw material an article for use which possesses a new or distinctive form, quality, or property." *Id.* at 11. The Court's cases suggest that the comparison of a claimed invention to a natural product must be comprehensive and thorough, and consider all relevant properties in determining whether an inventive conversion has been accomplished.

In view of these precedents, the Federal Circuit utilized an unduly narrow lens to compare the isolated DNA at issue with the naturally occurring genes. "We recognize that biologists may think of molecules in terms of their uses, but genes are in fact materials having a chemical nature and, as such, are best described in patents by their structures rather than by their functions." ***Ass'n for Molecular Pathology***, 689 F.3d. at 1330. This statement ignores the fact that the patent claims themselves merge structure with function. Claim 1 of U.S. Patent No. 5,747,282 is representative of this convergence when it claims "an isolated DNA coding for a BRCA1 polypeptide." Claim 2 of the same patent claims a cDNA molecule - which has a structure solely defined by its functional coding requirements.

The analytic error of focusing on structure to the exclusion of function is compounded by an idiosyncratic definition of the structural features that are accorded inventive weight. "[I]n nature, the claimed isolated DNAs are covalently bonded to such other materials. Thus, when cleaved, an isolated DNA molecule is not a purified form of a natural material, but a distinct chemical entity that is obtained by human intervention." *Id.* at 1329. The Federal Circuit erred in elevating the cleavage of a covalent bond during the excision of DNA into a transformative act that conferred patent eligibility. Instead, it is a routine technical operation that facilitates the removal of the gene from its native environment to an isolated state. Moreover, there is no basis in this Court's precedents for characterizing any specific chemical manipulation of natural subject matter as an eligibility-conferring maneuver.

The comparative analysis from the Federal Circuit overlooks several features of the isolated DNA at issue. The chemical cleavage that produces an isolated gene is not a manipulation that alters the intrinsic properties of the isolated product. The isolated DNA retains the naturally occurring nucleotide sequence, which the appellate court did not regard as relevant. "[I]t is the distinctive nature of DNA molecules as isolated compositions of matter that determines their patent eligibility rather than their physiological use or benefit." *Id.* at 1330. When the court declared that "the patent eligibility of an isolated DNA is not negated because it has similar informational properties to a different, more complex natural material," it failed to credit the fact that all of the chemical processing of the claimed DNA was actually driven by a genetic objective: to recover an isolated gene with an intact informational character. *Id.* No inventive conversion can be detected when the objective is simply to capture the naturally occurring genetic template and transport it outside the cell, and such repackaging cannot confer patent eligibility to the natural product. The isolated gene is thus more akin to the aggregated bacterial inoculant in *Funk Bros.*: "Even though it may have been the product of skill, it certainly was not the product of invention." *Funk Bros.*, 333 U.S. at 132.

The starting materials for the patent claims are the native BRCA1 and BRCA2 genes, and the processing that produces the claimed genes does not produce a nonnaturally occurring product, as both structure and function remain intact. There is no demonstration of the inventive conversion required by this Court for the patent eligibility of naturally-derived subject matter. As such, the isolated genes are products of nature, and do not constitute patentable subject matter.

IV. This Court's Precedent Requires That A Patent Not Exact More in Costs Than It Provides in Benefits

A. An Asymmetry Between Inventive Contribution and the Foreclosure of Innovation is Prohibited by *Mayo*

Just last year, in *Mayo*, this Court was very clear about the need to measure the potentially preemptive or inhibitory effect of a patent against the magnitude of any inventive contribution provided by its subject matter. "[T]he underlying functional concern here is a *relative* one: how much future innovation is foreclosed relative to the contribution of the inventor." *Mayo*, 132 S. Ct. at 1303 (italics in original). In the view of the Court, the most troubling scenario is presented when a patent involving a natural law or product but lacking any inventive contribution has an occlusive impact on technological innovation because it removes basic knowledge from the public domain. "And so there is a danger that the grant of patents that tie up their use will inhibit future innovation premised upon them, a danger that becomes acute when a patented process amounts to no more than an instruction to 'apply the natural law,' or otherwise forecloses more future invention than the underlying discovery could reasonably justify." *Id.* at 1301. To apply the *Mayo* formulation, the inventive contribution must be assessed, and compared to any foreclosure of innovation, in order to identify illegitimate patenting that exacts more in costs than it provides in benefits. The need for symmetry has been noted by this Court before. "The Patent Clause itself reflects a balance between the need to encourage innovation and the avoidance of monopolies which stifle competition without any concomitant advance in the 'Progress of Science and useful Arts.'" *Bonito Boats v. Thunder Craft Boats*, 489 U.S. 141, 146 (1989).

Mayo further considered how the discovery of natural laws and products were affected by the availability of patent rights, rejecting any invitation to lessen inventive standards in order to stimulate scientific discovery. *Mayo* explicitly recognized that even if patenting were to encourage research into laws of nature and basic scientific principles, the cost of patenting basic scientific knowledge would still be too high: "These statements reflect the fact that, even though rewarding with patents those who discover new laws of nature and the like might well encourage their discovery, those laws and principles, considered generally, are 'the basic tools of scientific and technological work.'" *Mayo*, 132 S. Ct. at 1301 (quoting *Benson*, 409 U.S. at 67). Patent rights are reserved for truly inventive work, and patent claims to natural laws and products controvert both *Mayo* and the essential patent bargain. "A patent by its very nature is affected with a public interest. As recognized by the Constitution, it is a special privilege designed to serve the public purpose of promoting the 'Progress of Science and useful Arts.'" *Precision Instrument Mfg. Co. v. Auto. Maint. Mach. Co.*, 324 U.S. 806, 816 (1944) (quoting U.S. CONST. art I, § 8, cl. 8).

The *Mayo* framework for granting patent rights for actual inventive achievement is broadly applicable to all patent claims, whether to products (*e.g.*, compositions of matter) or methods. Although *Mayo* was directed to the patent eligibility of method claims, the *Mayo* formulation is grounded in the underlying purposes of the patent system, and is not technology-specific or claim-dependent. Consequently, *Mayo*'s formulation can be squarely applied to the composition of matter claims at issue here.

B. Gene Patents Exemplify the Asymmetry Between Invention and Occlusion that *Mayo* Prohibits

The application of the *Mayo* formulation asks whether there is an inventive contribution that is commensurate with any foreclosure of innovation. In fact, this case reveals an acute asymmetry: the isolated BRCA1 and BRCA2 genes at issue are not invented, but the patenting of these genes has severely limited innovative development in the field of genetic testing, with adverse consequences for genetic medicine. Thus, this case is a paradigmatic illustration of the "danger" from illegitimate patenting that *Mayo* warned about.

First, as the foregoing analyses in *Parts II* and *III*, *supra*, have detailed, the "isolated DNA" claims are directed to or derived from naturally occurring wild-type or mutant forms of the BRCA1 and BRCA2 genes or, in the case of patent claims on DNA fragments, have a scope that can include naturally occurring genes. The presentation of a native gene as an "isolated DNA" molecule in the patent claims is the result of routine, well-established protocols in the field of molecular biology that do not alter or enhance the naturally occurring DNA sequence of the gene, and are conceptually analogous to the additional steps in the invalidated *Mayo* method claims which "add nothing of significance to the laws of nature." *Mayo,* 132 S. Ct. at 1299. Because the "isolated DNA" retains natural structure and function, the patent claims capture products of nature and preempt a law of nature.

The genes are basic scientific tools which have no effective substitutes. Rochelle C. Dreyfuss and James P. Evans, *From Bilski Back to Benson: Preemption, Inventing Around and the Case of Genetic Diagnostics,* 63 Stan. L. Rev. 1349, 1371 (2011). This fact only heightens the importance of rectifying the fact that such singular tools of biological science have been captured by patenting despite the absence of an inventive justification. The absence of any inventive contribution in the challenged patent claims violates the Court's standard for patentable subject matter, and provides the first part of the analysis for the *Mayo* formulation.

Second, the *Mayo* formulation requires an assessment of whether any foreclosure of innovation is the result of the patent grant. The patenting of DNA – as genes – removes critical scientific tools from widespread use in research and medicine by genetic scientists and medical practitioners, with adverse consequences for patients. The BRCA1 and BRCA2 genetic testing field is a signature example of how unjustified patent claims have exerted undue weight in limiting the development of breast cancer and ovarian cancer genetic medicine. The record in this case is replete with instances where scientists had to abandon the offering of genetic testing services, doctors could not provide genetic information as a part of medical care, and patients encountered limited or faulty genetic testing options for the BRCA1 and BRCA2 genes, all as a result of the restrictive climate created by these patents. *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 702 F. Supp. 2d 181, 205-207 (S.D.N.Y. 2010).

Genetic testing can be used to identify disease susceptibility, to establish diagnostic status, and to design personalized therapeutic regimens in medical care. Restrictive management of gene patents with critical diagnostic significance limits peer assessment, and reduces the available testing options for patients. Robert Cook Deegan et al., *Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers with Colon Cancers*, 12 Genetics in Medicine S15 (2010).

When a patent holder dominates a clinical field as the sole provider of genetic testing services, as Myriad has done for the BRCA1 and BRCA2 genes, patients are adversely affected. "Where patents and licensing practices have created a sole provider of a genetic test, patient access to those tests has suffered in a number of ways." The Secretary's Advisory Committee on Genetics, Health and Society (SACGHS), *Gene Patents and Licensing Practices and Their Impact on Patient Access* *to Genetic Tests* 3 (2010) [hereinafter "SACGHS"]. If the sole commercial provider of a particular genetic test does not offer a comprehensive genetic analysis, the test will not provide the most accurate assessment of genetic status, and compensatory genetic testing to correct deficiencies may be prohibited by the patent holder. An artificially constrained genetic testing climate can result in patients receiving incomplete test results that cannot be relied on for medical decision making. *Ass'n for Molecular Pathology,* 702 F. Supp. 2d at 206.

Myriad's limitations on commercial genetic testing for the BRCA1 and BRCA2 genes to determine the risk of hereditary breast and ovarian cancer have limited the ability of women to seek second opinions or confirmatory analysis of laboratory results. *Id.* at 207. This scenario is even more troubling because some of the patients receiving BRCA1 and BRCA2 genetic testing from Myriad had genetic mutations that were not detected by Myriad's testing protocols, and these women received false negative test results. Tom Walsh et al., *Spectrum of Mutations in BRCA1, BRCA2, CHEK2, and TP53 in Families at High Risk of Breast Cancer,* 295 J. Am. Med. Ass'n 1379, 1386 (2006). Where exclusive control of the relevant patent portfolio for a particular disease field has frustrated a competitive genetic testing environment - as is the case for the BRCA1 and BRCA2 genes - the consequences for patients are very real. The clinical standard of care becomes a function of the marketplace, rather than the laboratory, commercial objectives trump scientific merit, and patients encounter a distorted set of options for medical care. Eileen M. Kane, *Patent-Mediated Standards in Genetic Testing,* 2008 Utah L. Rev. 835, 849. This outcome highlights the importance of the patent eligibility questions posed by this litigation, and validates *Mayo*'s persistent focus on a cost-benefit analysis to determine the legitimacy of a patent grant.

It has been argued that gene patents are necessary to incentivize genetic research and the development of genetic tests. *Ass'n for Molecular Pathology*, 702 F. Supp. 2d at 211. The SACGHS undertook a comprehensive analysis on the need for and impact of patents affecting genetic testing, and asked whether the availability of patent rights stimulates scientific curiosity and engagement in genetic science. "[T]his information suggests that scientists are motivated to conduct genetic research by reasons other than patents, suggesting that discoveries will be sought regardless of the availability of intellectual property rights." SACGHS at 23. According to the SACGHS, the steady march of genetic research was not a patent-induced phenomenon. "[P]atents are not needed for much of U.S. basic genetic research to occur." *Id.* at 2.

Are gene patents essential for encouraging the development of in-house genetic testing services by commercial laboratories, such as for the BRCA1 and BRCA2 genetic tests? The SACGHS concluded that they were not. "[P]atent derived exclusive rights are neither necessary nor sufficient conditions for the development of genetic test kits and laboratory-developed tests. In the area of laboratory-developed tests particularly, where development costs are not substantial, patents were not necessary for the development of several genetic tests." *Id.* at 35. The genetic tests offered by Myriad fall into the latter category of laboratory-developed tests. Any assertions that the invalidation of gene patents will have devastating consequences on biomedical innovation cannot be reconciled with the empirical research demonstrating that gene patents do not incentivize much of the progress in genetic science and are not critical for the commercialization of testing services.

The lack of incentives provided by gene patents does not equate to an absence of impact when they have been granted. Gene patents, although unnecessary, are costly. This paradox only magnifies the harm created by the patenting of genes. Petitioners have amply demonstrated the limitations on research and patient care that have been created with the issuance of the BRCA1 and BRCA2 gene patents. Illegitimate gene patent claims in force have constrained the set of knowledge tools in the public domain, a consequence that has foreclosed innovation in the genetic testing field by imposition of a chilling effect. That was documented by the SACGHS in its review of Myriad's impact on the legal climate in which genetic research takes place. "Myriad therefore cannot fully elude responsibility for any chilling effect on research, because the company could fully anticipate that others would refrain from research for fear of being sued for infringement." SACGHS at A-27.

The concerns over the inhibitory effects of gene patenting received Congressional attention during the enactment of the America Invents Act of 2011 (AIA), Pub. L. 112–29 (2011). As a consequence, the AIA included a mandate that directed the United States Patent and Trademark Office to undertake a study on "effective ways to provide independent, confirming genetic diagnostic test activity where gene patents and exclusive licensing for primary genetic diagnostic tests exist." *Id.*, Section 27. Congress specifically asked for an assessment of "the impact that the current lack of independent second opinion testing has had on the ability to provide the highest level of medical care to patients and recipients of genetic diagnostic testing, and on inhibiting innovation to existing testing and diagnoses." *Id.* Legislative scrutiny of the consequences from issuing a specific class of patents – on human genes - is further evidence that such patents have an undue adverse impact on medical care.

The application of *Mayo's* formulation for identifying illegitimate patenting (invention vs. occlusion) leads to the inescapable conclusion that gene patenting has demonstrable costs, while failing to provide commensurate benefits. Moreover, available evidence has failed to document that gene patents have provided critical incentives for genetic medicine, further compounding the error of granting such patents. Gene patenting exhibits the asymmetry that *Mayo* warned about: the absence of any inventive contribution is coupled with a damaging effect on the ability of scientists and medical practitioners to freely utilize the most basic discoveries of genetic science, with adverse consequences for the development of innovative advances in genetic medicine.

The toll exacted on genetic science and medicine from the grant of illegitimate gene patents can be reversed by this Court's invalidation of the gene patent claims. Although both the executive branch (SACGHS) and the legislative branch (Congress) of the U.S. government have contended with limiting the harm created by gene patenting, this Court has the authority to squarely address the validity of gene patents by performing an exacting eligibility analysis of the challenged patent claims, using the standards that have been developed to define the boundaries of the patent system. While bioethical and human rights objections have been raised to the patenting of genes, it is clear that this Court's jurisprudence provides the basis for declaring that the discoveries of genetic science, including human genes, cannot be patented, in view of the law of nature and product of nature exclusions. The Court has an opportunity to restore the set of "basic tools" for genetic science, and to invalidate gene patenting for the benefit of scientists, medical practitioners, and patients who wish to use isolated genes in research and medical care. This Court's precise application of 35 U.S.C. § 101 will allow creative applications of fundamental knowledge to emerge and legitimately solicit legal protection, and ensure that the intellectual substrates for genetic science remain unowned.

CONCLUSION

For the foregoing reasons, the Court should reaffirm that patents may not issue for laws of nature or products of nature, and hold that the violation of these prohibitions invalidates patent claims to human genes under 35 U.S.C. § 101.

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AMICUS
CURIAE
BRIEF

RECORD
AND
BRIEFS

No. 12-398

FILED
JAN 31 2013
OFFICE OF THE CLERK

In The

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET. AL.,

Petitioners,

v.

MYRIAD GENETICS, INC., ET. AL.,

Respondents,

ON WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

BRIEF OF *AMICUS CURIAE* KNOWLEDGE ECOLOGY INTERNATIONAL IN SUPPORT OF PETITIONERS

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INTEREST OF AMICUS CURIAE[1]

Knowledge Ecology International ("KEI") is an international nonprofit, nongovernmental organization that searches for better outcomes, including new solutions, to the management of knowledge resources. In particular, KEI is focused on the management of these resources in the context of social justice. KEI is drawn to areas where current business models and practices by businesses, governments or other actors fail to adequately address social needs or where there are opportunities for substantial improvements. Among other areas, KEI has expertise in policies of both innovation in, and access to, medicines and medical technologies.

KEI is concerned about the implications of the Federal Circuit decision in the present case because of the far-reaching consequences for the future of patent law, innovation and the affordability of and access to medical technologies. As an advocate of new incentive and financing models for biomedical innovation and the proponent of several mechanisms for stimulating investments and promoting innovation outside of the patent regime, KEI has concerns that the Federal Circuit decision in the present case was incorrectly decided to the lower court's failure to take into account non-patent mechanisms to support and reward investments in the development of new products.

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[1] The parties have consented to the filing of this brief. Petitioners have lodged blanket consent to the filing of all *amicus* briefs. Respondent's consent to the filing of this amicus brief has been filed with the Clerk of Court. No counsel representing any party to the case authored this brief in whole or in part and no counsel or party made any monetary contribution to the preparation or submission of the brief.

SUMMARY OF THE ARGUMENT

The present case involves the patenting of human genes and isolated DNA. While the Constitution sets forth the rationale for the patent system, that is to promote the progress of science, blocking patents on products of nature have been granted by the United States Patent and Trademark. Human genes represent products of nature and their functions represent laws of nature. Their status as products of nature mean that they cannot be invented around and patents on such products preempt other uses, foreclosing further research and development, thereby hindering the progress of science. This Court has repeatedly rejected products of nature from the scope of patent-eligible subject matter because of their tendency to inhibit their use in making further discoveries and human genes should not be exempted from such exclusions.

Although proponents of liberal standards of patentability argue that patents are necessary to induce investments, such arguments ignore the numerous alternative, non-patent mechanisms that exist to reward investments into research and development. These alternative mechanisms are often used where patents represent and inappropriate or burdensome reward.

By design, gene patents are used to block secondary testing as well as research and development on diseases or diagnostics related to the patented sequences. The negative impact of patents has been justified on the ground that they are the only instrument that can adequately protect investments in research and development for new medical technologies. This assumption is false and a wide range of public policy instruments that are either currently in use, or have been proposed, to stimulate research and development for new medical products.

As diagnostics and personalized medicine become an increasingly important part of medical treatment, the freedom to undertake research and development on new tools is critical, as are the prices to the end users. If the Federal Circuit decision permitting patents on human genes stands, the proliferation of patents on genes will reduce the pace of research and narrow the direction of innovation which will, in turn, lead to high prices for patented technologies. Ultimately, allowing patents on human genes will negatively impact patients and treatment options, as well as future innovation.

ARGUMENT

I. PATENTING OF GENES IMPEDES THE CONSTITUTIONAL RATIONALE OF THE PATENT SYSTEM TO PROMOTE THE PROGRESS OF SCIENCE AND ALSO HARMS PUBLIC HEALTH.

The Constitution sets the basis for allowing Congress to create laws that permit limited time monopolies over their inventions. The rationale for permitting such monopolies is to "promote the Progress of Science and useful Arts." U.S. CONST. art. 1, §8, cl. 8. The purpose of a patent, then, is to advance scientific progress; the "embarrassment of an exclusive patent" is justified only because such monopolies serve the "benefit of society." *Graham v. John Deere Co.*, 383 U.S. 1, 7-10 (1966) (*quoting* Thomas Jefferson (internal citations omitted)).

While the Constitution grants Congress the authority to create patent laws, it also sets limits prohibiting the "overreach [of] the restraints imposed by the stated constitutional purposes." *John Deere Co.* at 6. This Court has specifically declared the Constitutional provision to be a "limitation. This qualified authority . . . is limited to the promotion of advances in the useful arts" and discoveries that do not promote the progress of science cannot be permitted. *Id.* It is critical to keep the Constitutional rationale of the patent system in mind and remember the limitations it sets in order to ensure the patent system does not improperly overreach and impede further research and development.

A. Products of Nature, Laws of Nature and Natural Phenomena, Such as the Human Genes, Are Not Patent-Eligible Because They Impede Innovation Rather than Promote It.

This Court, in applying Section 101 of the Patent Act to compositions of matter, has long held that three specific types of claims are categorically removed from patent eligibility. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980). These claims include "laws of nature, physical phenomena, and abstract ideas." *Id. See also Diamond v. Diehr*, 450 U.S. 175, 185 (1981); *Parker v. Flook* , 437 U.S. 584 (1978); *Gottschalk v. Benson*, 409 U.S. 67 (1972) *Funk Bros. Seeds Co. v. Kalo Co.*, 333 U.S. 127 (1948); *O'Reilly v. Morse*, 56 U.S. 112, 121 (1854); *LeRoy v. Tatham*, 55 U.S. 175 (1853). More recently, this Court reaffirmed these "long held" exclusions in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. __ , 132 S.Ct. 1289, 1293 (2012) (citations omitted). In eliminating these types of discoveries from patent protection, the Court notes their status as "basic tools of scientific and technological work" and that monopolization of such tools "might tend to impede innovation more than it would tend to promote it." *Id.*

In addition to excluding these broad categories from patentability, this Court has also made specific exclusions. For example, wood pulp and paper pulp were denied patent protection because they were known to be in existence prior to the patent claims. *American Wood Paper Co. v. Fiber Disintegrating Co.*, 90 U.S. 566 (1874). Relying on such jurisprudence, lower federal courts have made similar exclusions from patentability, particularly for materials or objects in merely purified form or that are obtained through extraction without further human processing. Lower courts have excluded from patentability purified uranium, *In re Marden*, 47 F.2d 957 (C.C.P.A. 1931), purified vanadium, *In re*

Marden, 47 F.2d 958 (C.C.P.A. 1931), purified tungsten, *Gen. Elec. Co. v. De Forest Radio Co.*, 28 F.2d 641 (3d Cir. 1928) and vitamin C purified from lemon juice, *In re King*, 107 F.2d 618 (C.C.P.A. 1939). In the aggregate, these cases demonstrate an exclusion of naturally occurring substances from patent eligibility.

The claims-at-issue in the particular case involve purified or isolated DNA. In other words, they represent products that are merely naturally occurring phenomena that have been obtained through extraction and not unlike the long line of cases rejecting such discoveries from patentability. While extraction requires human effort, such as the case with isolated DNA, such effort does not change the characteristic of the claims as non-patentable products of nature. The isolated BRCA genes are not markedly different from those found in nature and therefore not patentable. The limitation contained in the United States' patent system that excludes products of nature from patent protection serves to ensure that the Constitutional rationale for intellectual property is served: to promote the progress of science and the useful arts.

B. Where Patent Protection Improperly Preempts All Other Uses, the Progress of Science is Hindered and the Constitutional Rationale for Patents is Impeded

Preemption plays a critical role in determining whether a patent will promote or hinder the progress of science. This Court has therefore found that patents may not be granted where the effect of such a monopoly would "remove existent knowledge from the public domain, or to restrict free access to materials already available." *Graham v. John Deere Co.*, 383 U.S. 1, 5-6 (1966). Mere discovery of a naturally occurring substance, therefore, cannot receive patent protection. *Diamond v. Chakrabarty*, 447 U.S. 303, 312-13 (1980). Patented products of nature tend to be impossible to invent around and preempt all other uses. As such, they represents "manifestations of . . . nature, free to all men and reserved exclusively to none." *Id.* at 309 (citing *Funk Bros.*, 333 U.S. 130 (internal quotations omitted)).

In affirming the rejection of laws of nature, natural phenomena and abstract ideas from patentability, this Court has noted that permitting patents on such "basic tools" would run the "danger that the grant of patents that tie up their use will inhibit future innovation premised upon them." *Mayo v. Prometheus*, 566 U.S. __, 132 S.Ct. 1289, 1293 (2012)Where patents "tie up too much future use of laws of nature," monopoly protection cannot be afforded to such objects. *Id.* at 1302.

Monopolies prohibiting all others from creating the same effect or process by any other means discourages scientific progress, contravening the purpose of the patent system. *LeRoy v. Tatham*, 55 U.S. 156, 175 (1853). Preemption remains an important factor in determining the scope of patentability under Section 101 of the Patent Act. *See Bilski v. Kappos*, 130 S.Ct. 3218 (2010).

In the present case, patent protection on the BRCA genes completely forecloses and preempts all other uses, thereby contravening the purpose of the patent system. Patents on human DNA have been called "blocking" patents that represent "unnecessary toll booths on the road to discovery." Alan E. Guttmacher, et. al., *Genomic Medicine—A Primer*, 347 NEW. ENG. J. MED. 1512, 1514 (2002). Human genes, like other products of nature, are extremely difficult, if not impossible, to invent around. *See* Isabelle Huys, et. al., *Legal Uncertainty in the Area of Genetic Diagnostic Testing*, 27 NATURE BIOTECHNOLOGY 903, 907 (2009). Human genes are obvious products of nature, their functions represent laws of nature, and this Court has repeatedly rejected patentability of such objects because of "a concern that patent law not inhibit further discovery by improperly tying up the future use of laws of nature." *Prometheus v. Mayo*, 566 U.S. __, 132 S.Ct. 1289, 1301 (2012). Gene patents thus completely foreclose future research on the effects of the DNA sequences and scientists cannot conduct research on the naturally occurring gene. Patent protection therefore should not extend to isolated DNA.

C. Patenting of Human Genes Harms Genetic Research, Medical Innovations and the Future of Public Health.

The patenting of human genes tends to foreclose future research on the gene and also hinders alternative testing for BRCA mutations.

Scientists and researchers have expressed reluctance to conduct research and development where patents on genes exist because of the fear of possible patent infringement suits. As a result, research on the diseases associated with the genes and development of better diagnostic testing is likely to be forestalled.

Patients will, predictably, face harm as a result of the Federal Circuit ruling. Myriad is currently the sole provider of diagnostic testing for mutations of the BRCA1 and BRCA2 genes and can therefore charge a monopoly price. Some insurance companies do not cover the test and patients must then decide whether to pay the high monopoly price of more than $3,000 or forego the diagnostic. Myriad's monopoly over the genes prevent second opinion testing.

In addition to placing a high price on its diagnostic test, Myriad's exclusive monopoly over the genes prohibits all research on the BRCA1 and BRCA2 genes. Patients are benefited from continued research and development to improve diagnostic testing. In fact, Myriad's test was shown to have a twelve-percent error rate and also failed to identify all known mutations of the gene. *See* Tom Walsh, et. al., *Spectrum of Mutations in BRCA1, BRCA2, CHECK2 and TP53, in Families at High Risk of Breast Cancer*, 295 JAMA 1369, 1386 (2006). As a result, the exclusive monopoly over the BRCA genes prevented patients from accessing more accurate or comprehensive testing.

II. NON-PATENT MECHANISMS CAN AND SHOULD ENCOURAGE PROGRESS WHERE PATENTS ARE AN INAPPROPRIATE, UNNECESSARY, INSUFFICIENT, OR BURDENSOME REWARD

One of the most common justifications for liberal standards on patentability are those that assert, without evidence, that patents are necessary to protect and reward investments in the development of new products. However, this argument fails to take into account the known shortcomings of patents as incentive mechanisms. It also ignores the growing proliferation of alternative, non-patent mechanisms used to stimulate research and development. A wide range of incentives to induce investment into research and development exist or can be implemented as alternatives to exclusive monopoly rights.

In certain areas of innovation, patents do not provide adequate incentives for research or harm future progress. In such cases, other mechanisms to reward innovation may be needed.

In the present case, and as concluded in a report conducted by the Department of Health and Human Services Advisory Committee on Genetics, Health, and Society, gene patents were unnecessary in providing incentives for research and development of clinical testing. Dep't. of Health & Human Services, Sec'y's Advisory Comm. On Genetics, Health and Soc'y, *Gene Patents and Licensing*

Practices and Their Impact on Patient Access to Genetic Tests (Apr. 2010), *available at* http://oba.od.nih.gov/oba/sacghs/reports/SACGHS_patents_report_2010.pdf. In fact, gene patents have harmed patient access to genetic diagnostic testing and have also denied quality assurance of the tests. *Id.* Patents thus represent an inappropriate and burdensome incentive in the context of isolated DNA or human genes and other, more appropriate mechanisms, should be explored.

A wide range of non-patent incentives to promote research and development exist.[2] These mechanisms, used to induce investment into innovation across broad sectors, often take the place of patent incentives. Trade secrets, for example, and while possessing their own shortcomings in terms of limiting access to knowledge, are used to promote investments in medical products, including in particular, developments for medical diagnostic technologies and biotechnology drugs. Iraj Daizadeh, et. al., *A general approach for determining when to patent, publish, or protect information as a trade secret*, 20 NAT. BIOTECH 1053-1054 (2002).

In addition, a wide range of *sui generis* forms of intellectual property exist, often used in parallel to the patent system and implemented where patent protection is unavailable. One commonly used *sui generis* protection is the application of time limited exclusive rights to rely on clinical test data used to register new drugs or vaccines. Food, Drug and Cosmetics Act, New Drugs, 21 U.S.C. §355. These rights include five years of test data protection for new chemical entity pharmaceutical products, an additional three years of protection where a new indication for an existing product is found, and twelve years for new biologic drugs. *Id.*

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[2] *Amicus curiae* does not necessarily endorse the alternative reward mechanisms discussed herein. This listing of alternative mechanisms to induce research and development or reward inventors serves only to illustrate the wise range of alternatives that can be used where patents are not available or represent inappropriate incentives.

Another example of a non-patent reward is the additional five years of market exclusivity granted to encourage research on antibiotic resistance. S.3187, Generating Antibiotic Incentives Now (GAIN), Food & Drug Administration Safety and Innovation Act, 112th Cong., 21 U.S.C. §355(v) (2012). Additional marketing exclusivity is similarly granted for the development of new drug indications for rare, "orphan" diseases or to reward investments in clinical trials for pediatric patents. Internal Revenue Code, Clinical testing expenses for certain drugs for rare diseases or conditions, 26 U.S.C. §45C. with a fifty-percent tax credit.

To stimulate research and development for treatments on rare tropical diseases, Congress created a "Priority Review Voucher" providing for a transferable right to an accelerated consideration of new drug approvals as a reward for registering drugs to treat rare diseases such as cholera or leprosy. Food, Drug and Cosmetic Act, Priority Review to Encourage Treatments for Tropical Diseases, 21 U.S.C. §360n.

In addition to these existing and expanding mechanisms, a new class of rewards to induce investment in medical research and development are under consideration, both international and domestically. This new class involves cash innovation inducement prizes to stimulate investments in the public health and other areas of public and private interests. *See, e.g.*, James Love & Tim Hubbard, *Prizes for Innovation of New Medicines and Vaccines*, 18 ANNALS HEALTH L. 155 (2009); James Love, *The role of Prizes in Developing Low-Cost, Point of Care Rapid Diagnostic Tests and Better Drugs for Tuberculosis*, KNOWLEDGE ECOLOGY INTERNATIONAL (2008), *available at* http://www.keionline.org/misc-docs/Prizes/prize_tb_msf_expert_meeting.pdf; Ron Marchant, *Managing Prize Systems*, 2 KNOWLEDGE ECOLOGY STUDIES (2008); J. G. Morgan, *Inducing Innovation Through Prizes*, 3 INNOVATIONS: TECHNOLOGY, GOVERNANCE, GLOBALIZATION 105 (2008); L. Brunt, et. al., INDUCEMENT PRIZES AND INNOVATION (2008); Bruce G. Charlton, *Mega-Prizes in Medicine: Big Cash Awards May Stimulate Useful and Rapid Therapeutic Innovation*, 68 MEDICAL HYPOTHESES 1-3 (2007); James Love & Tim Hubbard, *The Big Idea: Prizes to Stimulate R&D for New Medicines*, 82 CHI.-KENT L. REV. 1519, 1521-24 (2007); T. Kalil, *Hamilton Project and Brookings Institution, Prizes for Technological Innovation* (2006); Joseph E. Stiglitz, *Scrooge and Intellectual Property Rights: A Medical Prize Fund Could Improve the Financing of Drug Innovations*, 333 BRITISH MEDICAL JOURNAL 129 (2006); Julien Penin, *Patents Versus Ex Post Rewards*, 34 RESEARCH POL'Y 641 (2005); W. A. Masters, *Prizes for Innovation in African Agriculture* (2004), *available at* http://www.eart.columbia.edu/cgsd/prizes; K. Davidian, PRIZES, PRIZE CULTURE AND NASA'S CENTENNIAL CHALLENGES (2004); Burton Weisbrod, *Solving the Drug Dilemma*, WASH. POST at A21 (Aug. 22, 2003); Brian D. Wright, *The Economics of Invention Incentives: Patents, Prizes and Research Contracts*, 73 AM. ECON. REV. 691 (1983).

Domestically, in the 112th Congress, two bills were introduced in the Senate that proposed large cash prizes as an alternative to an exclusive patent monopoly, including S. 1137 and S. 1138. Medical Innovation Prize Fund Act, S.1137, 112th Cong. (2011); Prize Fund for HIV/AIDS Act, S.1138, 112th Cong. (2011). One of these bills would apply to all pharmaceutical drugs, while the other would limit its application to HIV/AIDS drugs.

This approach has been favored by a number of experts and on May 15, 2012, the U.S. Senate Committee on Health, Education, Labor and Pensions (HELP) held a hearing on one of the prize fund bills, S.1138. Nobel Prize winner, Joseph Stiglitz, noted in his testimony at this hearing that the patent system may "have adverse effects on innovation, because the most important input into any research is prior ideas . . . there is a simple way to 'square the circle,' which entails de-linking research and development incentives from drug price . . . It does this through a simple mechanism—prizes." Joseph E. Stiglitz, Testimony to the U.S.

Senate HELP Committee, Subcommittee on Primary Health and Aging, Hearing on the High Cost of High Prices for HIV/AIDS Drugs and the Prize Fund Alternative, *available at* http://www.help.senate.gov/imo/media/doc/Stiglitz.pdf.

In addition to the domestic proposals for prizes, cash inducement funds have gained support in the international community as well. For example, the World Health Organization has called for new proposals to incentivize research and development "addressing the de-linkage of the costs of research and developments and the price of health products and methods for tailoring the optimal mix of incentives to a particular condition or product with the objective of addressing diseases that disproportionate affect developing countries." Global strategy and plan of action on public health, innovation and intellectual property, World Health Assembly 61.21 (2008). Such de-linkage includes the awards of prizes. *Id.* at Annex, element 5.3(a).

Prizes may be particularly relevant in areas where products are not eligible for patents or where it would be inefficient or harmful to permit exclusive monopoly rights to be enforced. Areas where unrestricted access to basic information or discoveries is critical to the progress of science, patents act as a barrier to further innovation and do more harm than good. *See* John Sulston & Georgina Ferry, THE COMMON THREAD (2003); Aaron S. Kesselhein & Jerry Avorn, *University Based Science and Biotechnology Products: Defining the Boundaries of Intellectual Property*, 293 JAMA 850-54 (2005).

In the present case, patents are not an appropriate mechanism for rewarding investments in the isolation of DNA or the identification of genes because of their status as products of nature as well as their effect as a blocking patent. Human genes and other products of nature represent upstream objects and are necessary to future innovation and if patented would have the same clear, adverse effect on innovation that Stiglitz describes. Patents in the area of human genes are burdensome, foreclosing future research and development and preempting all other uses of the gene in direct contradiction to the purposes of the patent system. More viable, alternative reward mechanisms exist and if incentives are necessary, these alternatives should be used to induce investment into research and development in this area instead of patents.

CONCLUSION

The United States patent system operates to provide incentives for research and development, but is not without its limits. Where patents hinder progress rather than promote it, they represent an inappropriate reward. For the reasons stated above, this Court should reverse the decision of the Federal Circuit and rule that human genes are not patentable.

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January 31, 2013.

AMICUS
CURIAE
BRIEF

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OFFICE OF THE CLERK

No. 12-398

In The
Supreme Court of the United States

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THE ASSOCIATION FOR
MOLECULAR PATHOLOGY, ET AL.,

Petitioners,

v.

MYRIAD GENETICS, INC., ET AL.,

Respondents.

◆

**On Writ of Certiorari to the
United States Court of Appeals
for the Federal Circuit**

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BRIEF FOR *AMICUS CURIAE* ERIC S. LANDER IN SUPPORT OF NEITHER PARTY

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STATEMENT OF INTEREST OF *AMICUS CURIAE*[*]

***Amicus Curiae* Eric S. Lander** was one of the principal leaders of the Human Genome Project (HGP), the international project that determined and made freely available the DNA sequence of the human genome. Dr. Lander directed the largest center in the HGP, which generated approximately one-third of the human genome sequence.

Dr. Lander is a geneticist, molecular biologist and mathematician. He serves as President and Founding Director of the Broad Institute of Harvard and MIT, a nonprofit biomedical research institution focused on genomic medicine. He is also Professor of Biology at the Massachusetts Institute of Technology and Professor of Systems Biology at Harvard Medical School. In addition, he has been a founder of several biotechnology firms.

Dr. Lander was elected a member of the U.S. National Academy of Sciences in 1997 and a member of the U.S. Institute of Medicine in 1999. He has received numerous major international awards for his research on the human genome.

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[*] Counsel for all parties have consented to the filing of this brief, and their consents have been lodged with the Clerk of this Court. No counsel for any party had any role in authoring this brief, and no person other than the named *amicus* and his counsel has made any monetary contribution to the preparation and submission of this brief. *See* Rule 37.

Dr. Lander also serves as Co-Chair of the President's Council of Advisors on Science and Technology (PCAST), an advisory group consisting of some of the nation's leading scientists and engineers, who directly advise the President and the Executive Office of the President. Importantly, however, Dr. Lander wishes to emphasize that this brief represents his own personal views. The brief is in no way intended as a statement of policy or position by the United States Government, the Broad Institute, Harvard, MIT, or any other entity.

In this case, the Federal Circuit held, among other things, that claims to isolated DNA fragments recite a composition of matter patent-eligible under 35 U.S.C. § 101. The assumption underlying this holding is that such fragments do not occur in Nature. As a leading genomic researcher, Dr. Lander has a strong interest in advising the Court that, in fact, such fragments routinely occur in Nature and that claims to such fragments create an insurmountable barrier to scientific innovation.

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SUMMARY OF THE ARGUMENT

This case hinges on a scientific question: whether DNA fragments from a human chromosome are (1) products of Nature or (2) at least *similar enough* to products of Nature that they should not be considered "markedly different." *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980).

The members of the Federal Circuit panel below agreed that the DNA of a *whole* human chromosome was a product of Nature. But the majority held that isolated DNA *fragments* of a human chromosome were *not* products of Nature.

Because the majority made (without citing scientific support) a foundational assumption that isolated DNA fragments of the human genome do not *themselves* routinely occur in Nature, it considered whether they are *similar enough* to products of Nature. Employing analogies, the panel members debated whether isolated DNA cleaved from a chromosome was akin to a leaf plucked from a tree, or a kidney surgically removed from a human body.

This reasoning-by-analogy was unnecessary because the majority's foundational assumption is demonstrably incorrect: it is well-accepted in the scientific community that (a) chromosomes are constantly being broken into DNA fragments by natural biological processes that break the covalent bonds within DNA chains; (b) these DNA fragments are ubiquitous in the human body, both within cells and in cell-free blood, urine, sputum and stool; and (c) these fragments cover the entire human genome and, in particular, include the BRCA1 and BRCA2 genes claimed by Myriad's patents. Myriad's claims thus include DNA fragments that are unambiguously products of Nature.

Under this Court's interpretation of 35 U.S.C. § 101, composition-of-matter patents on such preexisting products of Nature are not permissible. Such products of Nature are "manifestations of . . . nature, free to all men and reserved exclusively to none." *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948).

A patent on a product of Nature would authorize the patent holder to exclude everyone from observing, characterizing or analyzing, *by any means whatsoever*, the product of Nature. This barrier is inherently insurmountable: one cannot study a product of Nature if one cannot legally possess it. A molecule is one of the "basic tools" – indeed, the *essential* tool – for studying the molecule itself. *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972). A patent on a molecule that is a product of Nature would thus authorize a patent holder to wall off an entire domain of Nature from observation.

Finally, the majority held that a decision that isolated DNA fragments of the human genome are patent-ineligible would disrupt long-settled expectations and could wreak havoc on the biotechnology industry. The majority's concern is unfounded.

Most biotechnology products are protected by patents on *non-natural* DNA molecules, rather than *naturally occurring* genomic DNA. The biotechnology industry would not be substantially affected by a narrowly crafted decision here holding that (1) fragments of human genomic DNA are patent-ineligible where the scientific evidence is clear that the claimed molecules themselves are routinely found in Nature and where the process for purification or synthesis of such molecules is routine but (2) human cDNAs are patent-eligible, because these molecules do not occur in Nature and have clearly different functional properties from related products of Nature.

On the contrary, such a narrowly crafted decision would foster scientific progress and technological innovation by guaranteeing an unfettered ability to study a remarkable product of Nature – the human genome. This ability will lead to countless discoveries about human disease, as well as an outpouring of medical invention with enormous consequences for human health.

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ARGUMENT

This *amicus* brief provides information and perspective concerning several scientific issues at the center of the case – namely, whether (1) isolated DNA fragments of the human genome are products of Nature; (2) patents that foreclose the observation, characterization or analysis of products of Nature impede scientific progress and technological innovation; and (3) a narrowly crafted decision that isolated DNA fragments of the human genome are patent-ineligible would disrupt the biotechnology industry or instead would foster innovation

I. THE FEDERAL CIRCUIT INCORRECTLY ASSUMED, WITHOUT CITING SCIENTIFIC EVIDENCE, THAT ISOLATED DNA FRAGMENTS OF THE HUMAN GENOME DO NOT OCCUR IN NATURE, WHEN IT IS WELL-ACCEPTED IN THE SCIENTIFIC COMMUNITY THAT THEY DO.

The human genome consists of 23 pairs of chromosomes, which together specify the instructions for life and harbor variations that can predispose to disease. Each chromosome contains a long DNA double helix, totaling approximately 3 billion nucleotides in length. The term "gene" typically refers to a nucleotide sequence, within a chromosome, that encodes instructions for proteins.[1]

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[1] Myriad's patents concern the BRCA1 and BRCA2 genes. The BRCA1 gene, for example, consists of a region of ~81,000 nucleotides on Chromosome 17, which is 68 million nucleotides long. Todd M. Smith et al., *Complete Genomic Sequence and Analysis of 117 kb of Human DNA Containing the Gene BRCA1*, 6 Gen. Res. 1029 (1996); Eric S. Lander et al., *Initial Sequencing and Analysis of the Human Genome*, 409 Nature 860 (2001). The BRCA1 gene is transcribed into an initial RNA molecule, which is then spliced to yield a shorter mature RNA molecule and translated into the BRCA1 protein. Certain variations in the DNA sequence of the BRCA1 gene ("spelling differences") predispose women carrying them to develop early-onset breast cancer. The BRCA2 gene is on chromosome 13.

A. Myriad's patents cover isolated DNA fragments from the human genome.

Myriad's claims on the BRCA1 gene create a monopoly on any "isolated DNA" containing "at least" 15 consecutive bases from any DNA sequence that encodes a BRCA1 protein[2,3] – including from the human BRCA1 gene itself.

In the context of Myriad's patents, "isolated DNA" refers to "a free-standing portion of a larger, natural DNA molecule. Isolated DNA has been cleaved (*i.e.*, had covalent bonds in its backbone chemically severed) or synthesized to consist of just a fraction of a naturally occurring DNA molecule." *Association for Molecular Pathology v. United States Patent & Trademark Office*, 689 F.3d 1303, 1328 (Fed. Cir.), *cert. granted sub nom. Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 694 (2012). Isolated DNA has the identical nucleotide sequence as in the larger whole; it differs only in having been cleaved from the whole.

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[2] Claim 5 of the main patent at issue states: "5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1." U.S. Patent No. 5,747,282 (issued May 5, 1998) ("'282 patent") col. 153 ll.66-67. Claim 1, in turn, describes the DNA of the full BRCA1 gene: "1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2." '282 patent col. 153 ll.57-59.

[3] We focus our arguments on claims regarding BRCA1. However, they apply *mutatis mutandis* to the analogous claims regarding BRCA2 in U.S. Patent No. 5,837,492 (issued November 17, 1998).

"Isolated DNA" thus refers not simply to *physical purification*,[4] but to a molecule that is *chemically distinct* from the larger DNA molecule of the entire chromosome. The Federal Circuit wrote that "isolated DNA is not just purified DNA. Purification makes pure what was the same material, but was combined, or contaminated, with other materials [whereas] . . . isolated DNA . . . has also been manipulated chemically [i.e., cleaved from a larger DNA]. . . ." 689 F.3d at 1328.

Myriad's claims to "isolated DNA" fragments of the human genome are extremely broad. They include any DNA fragment of chromosome 17 that contains *at least* 15 nucleotides of the region containing the BRCA1 gene. These fragments range in length from

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[4] "Purification" of an isolated DNA molecule from a mixture of other isolated DNA molecules has been straightforward since the invention in the 1970s of recombinant DNA ("gene cloning"). A molecular biologist can create a "library" of DNA molecules by (i) attaching genomic DNA fragments *en masse* to "vector" molecules, (ii) transferring the resulting molecules *en masse* into bacteria and (iii) growing the resulting bacteria on Petri plates. This process yields millions of separate bacterial colonies, each carrying an *individual* segment of DNA from the human genome. In this way, the first human recombinant library, produced in 1978, successfully "purified" all the fragments of the human genome from one another. Tom Maniatis et al., *The Isolation of Structural Genes from Libraries of Eucaryotic DNA*, 15 Cell 687 (1978); Richard M. Lawn et al., *The Isolation and Characterization of Linked Delta- and Beta-globin Genes from a Cloned Library of Human DNA*, 15 Cell 1557 (1978). Since then the challenge has thus not been purifying the fragments, but discovering their function.

15 nucleotides to nearly the *whole chromosome*.[5] In total, the claims cover more than *one quadrillion* distinct fragments from chromosome 17. *See* Fig. 1.

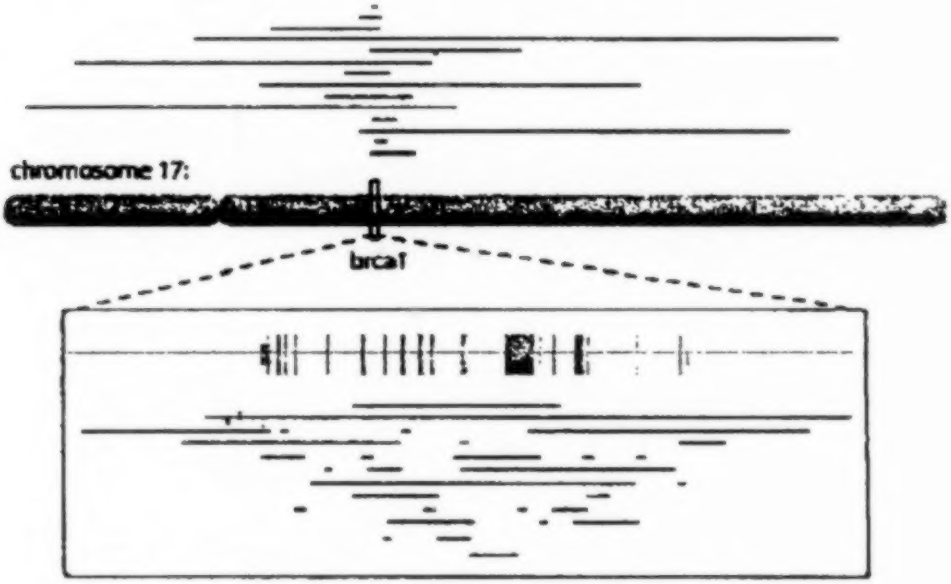

Figure 1: Examples of the many fragments of "isolated DNA" claimed by Myriad's patent on BRCA1. The fragments range in length from 15 nucleotides to many millions of nucleotides, and include any fragment that contains 15 nucleotides of the BRCA1 gene region.

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[5] The concurrence below vastly understated the breadth of Myriad's claim 5. *See* 689 F.3d at 1341 ("I begin with the short isolated sequences such as those covered by claim 5 which is directed to 'an isolated DNA having at least 15 nucleotides of the DNA of claim 1.' This claim covers a sequence as short as 15 nucleotides and arguably as long as the *entire gene*." (emphasis added)). An isolated DNA fragment containing *virtually all of chromosome 17* qualifies as "an isolated DNA having at least 15 nucleotides of the DNA of claim 1."

B. The Federal Circuit assumed, without citing scientific evidence, that isolated DNA fragments of the human genome do not occur in Nature and therefore inappropriately used reasoning-by-analogy to decide whether such fragments are "similar" to or "markedly different" from products of Nature.

The central issue in the Federal Circuit's decision was (1) whether DNA fragments from a human chromosome are products of Nature or (2) if they are *not* products of Nature, whether they are *similar enough* to products of Nature that they cannot be considered "markedly different." *Chakrabarty*, 447 U.S. at 310.

The judges agreed that the DNA of a *whole* human chromosome was the patent-ineligible handiwork of Nature,[6] but they disagreed as to the status of an *isolated DNA fragment* of a human chromosome.[7]

The Federal Circuit began its analysis with a foundational assumption that the isolated DNA fragments claimed by Myriad (such as those shown in Figure 1) do not themselves occur in Nature:

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[6] *See* 689 F.3d at 1328, 1343 n.6, 1350.

[7] *See* 689 F.3d at 1325-33, 1340-43, 1350-58.

> The isolated DNA molecules before us are not found in nature. . . . In this case, the claimed isolated DNA molecules do not exist in nature within a physical mixture to be purified. They have to be chemically cleaved from their native chemical combination with other genetic materials. In other words, in nature, the claimed isolated DNAs are *covalently bonded* to such other materials. Thus, when cleaved, an isolated DNA molecule is not a purified form of a natural material, but a distinct chemical entity that is obtained by human intervention.

689 F.3d at 1325, 1329 (emphasis added).

The Federal Circuit cited no scientific support for its assertion that the claimed isolated DNA fragments do not occur in Nature.

Proceeding from this assertion, the Federal Circuit then sought to determine whether such isolated DNA fragments are fundamentally *similar* to products of Nature or are markedly "different from the natural products in 'name, character, and use.'" *Id.* at 1329 (quoting *Chakrabarty*, 447 U.S. at 309-10). The panel members debated whether cleaving a DNA fragment from a chromosome was akin to plucking a leaf from a tree, or surgically removing a kidney from a human body. *Id.* at 1332, 1347, 1352-53. Further, the panel members disagreed internally regarding whether the breaking of chemical covalent bonds rendered the fragments "materially different" from naturally occurring DNA. *Compare id.* at 1329-30 *with id.* at 1341 (Moore, J., conc.) *and id.* at 1350 (Bryson, J., conc. in part and diss. in part).

As shown in the next section, the Federal Circuit had no need to engage in this reasoning-by-analogy because the foundational assertion that the DNA fragments themselves do not occur in Nature is demonstrably incorrect.

C. It is well-accepted in the scientific community that isolated DNA fragments of the human genome – including many fragments covered by Myriad's patents – occur routinely in the human body and thus are products of Nature.

It has been well established for over 30 years that isolated DNA fragments of human chromosomes routinely occur in the human body. Moreover, these isolated DNA fragments span the entire human genome, including the BRCA1 and BRCA2 genes. Some of the abundant scientific evidence is summarized below.

Cell death occurs routinely in the human body, with many billions of cells dying every day.[8] When cells die, chromosomal DNA is broken into fragments as part of a carefully orchestrated natural process.[9] Nature provides the cell with specialized DNA-cleaving enzymes (called endonucleases); during cell death and other critical cellular processes, these enzymes have the specific function of breaking covalent bonds that otherwise hold together the DNA chain.[10]

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[8] Andrew G. Renehan et al., *What is Apoptosis, and Why Is It Important?*, 322 Br. Med. J. 1536 (2001).

The proper control of this natural process is so important that mutations that disrupt DNA-cleaving enzymes are associated with disease. For example, mutations that reduce the activity of a particular DNA-cleaving enzyme (called DNAse I) have been linked to the auto-immune disease lupus.[11] In another example, patients who lack either of two other genes encoding DNA-cleaving enzymes (involved in repairing DNA damage from ultraviolet light) have a serious disease called xeroderma pigmentosum, which often causes skin cancer.[12]

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[9] Jerry R. Williams et al., *Association of Mammalian Cell Death with a Specific Endonucleolytic Degradation of DNA*, 252 Nature 754 (1974).

[10] Xuesong Liu et al., *The 40-kDa Subunit of DNA Fragmentation Factor Induces DNA Fragmentation and Chromatin Condensation During Apoptosis*, 95 Proc. Natl. Acad. Sci. 8461 (1998).

[11] Hyoung Doo Shin et al., *Common DNase I Polymorphism Associated with Autoantibody Production Among Systemic Lupus Erythematosus Patients,* 13 Hum. Mol. Genet. 2343 (2004).

[12] Anneke M. Sijbers et al., *Xeroderma Pigmentosum Group F Caused by a Defect in a Structure-Specific DNA Repair*

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Isolated DNA fragments are not only present in cells, but also routinely found in cell-free blood. The quantity of freely circulating DNA fragments is especially high in the blood of many cancer patients.[13] Such fragments have also been found in substantial quantities in the blood of patients with viral infections,[14] exercise overtraining,[15] trauma,[16] and stroke,[17] and during pregnancy.[18]

The presence of freely circulating isolated DNA fragments in the blood is common enough that it can

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Endonuclease, 86 Cell 811 (1996); Thierry Nouspikel et al., *Mutations That Disable the DNA Repair Gene XPG in a Xeroderma Pigmentosum Group G Patient*, 3 Hum. Mol. Genet. 963 (1994).

[13] Maurice Stroun et al., *Isolation and Characterization of DNA from the Plasma of Cancer Patients*, 23 Eur. J. Cancer. Clin. Onc. 707 (1987).

[14] Tran Thi Ngoc Ha et al., *Elevated Levels of Cell-Free Circulating DNA in Patients with Acute Dengue Virus Infection*, 6 PLoS1 e25969 (2011).

[15] Ioannis Fatouros et al., *Cell-Free Plasma DNA as a Novel Marker of Aseptic Inflammation Severity Related to Exercise Overtraining*, 52 Clin. Chem. 1820 (2006).

[16] Nicole Y.L. Lam et al., *Time Course of Early and Late Changes in Plasma DNA in Trauma Patients*, 49 Clin. Chem. 1286 (2003).

[17] Timothy H. Rainer et al., *Prognostic Use of Circulating Plasma Nucleic Acid Concentrations in Patients with Acute Stroke*, 49 Clin. Chem. 562 (2003).

[18] H. Christina Fan et al., *Analysis of the Size Distributions of Fetal and Maternal Cell-Free DNA by Paired-End Sequencing*, 56 Clin. Chem. 1279 (2010).

be used for identifying genomic mutations in diseases such as cancer and cystic fibrosis.[19]

Studies of isolated DNA fragments in human blood have found that the fragments have a wide range of sizes. Fragments ranging from more than 80,000 bases to fewer than 100 bases are commonly seen.[20]

In pregnancy, both maternal and fetal DNA are found in the blood of the mother, with fragments smaller than 150 bases observed.[21] The presence of isolated fragments of fetal DNA in maternal blood has resulted in the ability to diagnose fetuses for chromosomal disorders (such as Down Syndrome) through sequencing of fetal DNA in maternal blood.[22]

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[19] George D. Sorenson et al., *Soluble Normal and Mutated DNA Sequences from Single-copy Genes in Human Blood*, 3 Cancer Epidemiol. Biomarkers Prev. 67 (1994).

[20] Mary Beth Giacona et al., *Cell-Free DNA in Human Blood Plasma: Length Measurements in Patients with Pancreatic Cancer and Healthy Controls*, 17 Pancreas 89 (1998); Florent Mouliere et al., *High Fragmentation Characterizes Tumour-Derived Circulating DNA*, 6 PLoS1 e23418 (2011).

[21] H. Christina Fan et al., *Analysis of the Size Distributions of Fetal and Maternal Cell-Free DNA by Paired-End Sequencing*, 56 Clin. Chem. 1279 (2010).

[22] H. Christina Fan et al., *Noninvasive Diagnosis of Fetal Aneuploidy by Shotgun Sequencing DNA from Maternal Blood*, 105 Proc. Natl. Acad. Sci. 16266 (2008).

Multiple studies[23] in leading journals have shown that the isolated DNA fragments in blood are so prevalent and cover the human genome so completely that it is "possible to unambiguously determine the whole genome sequence of a fetus from a teaspoon's worth of maternal blood."[24]

Inspection of the publicly available DNA sequence data from two of these studies confirms that (as expected) the isolated fragments of fetal DNA in maternal blood cover the BRCA1 and BRCA2 genes – and therefore include many of the isolated DNA fragments covered by Myriad's patents.[25]

Finally, the presence of isolated DNA fragments of human chromosomes is not limited to intact cells and cell-free blood. DNA fragments are so pervasive as to be found in urine,[26] sputum[27] and stool.[28] Much research effort, both in the public and private sector, is underway to take advantage of the availability of these cell-free DNA fragments for diagnostic testing.[29]

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[23] H. Christina Fan et al., *Non-invasive Prenatal Measurement of the Fetal Genome*, 487 Nature 320 (2012); Jacob O. Kitzman et al., *Noninvasive Whole-Genome Sequencing of a Human Fetus*, 4 Sci. Transl. Med. 137ra76 (2012); Y.M. Dennis Lo et al., *Maternal Plasma DNA Sequencing Reveals the Genome-Wide Genetics and Mutational Profile of the Fetus*, 2 Sci. Transl. Med. 61ra91 (2010).

[24] Diana W. Bianchi et al., *Fetal Genes in Mother's Blood*, 487 Nature 304 (2012).

[25] BRCA1 and BRCA2 data from H. Christina Fan et al., *Non-invasive Prenatal Measurement of the Fetal Genome*, 487 Nature 320 (2012), are available at http://www.stanford.edu/~quake/brca. Data for Kitzman et al., *Noninvasive Whole-Genome Sequencing of a Human Fetus*, 4 Sci. Transl. Med. 137ra76 (2012), are available at the Genotypes and Phenotypes (dbGaP) database of the National Center for Biotechnology Information at the National Institutes of Health (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap, accession number phs000500.v1.p1).

In sum, it is well-accepted in the scientific community that (a) chromosomes are constantly being broken into DNA fragments by natural biological processes that break the covalent bonds within DNA chains; (b) these DNA fragments can be routinely found in the human body, within cells (both living and dying) as well as in cell-free blood, urine, sputum and stool; and (c) these fragments cover the entire human genome and, in particular, include many of the DNA fragments claimed by Myriad's patents.

The Federal Circuit thus erred with respect to the central issue in its analysis: isolated DNA fragments from the human genome, including those essential for determining a woman's risk of early-onset breast cancer and claimed in Myriad's patents, are products of Nature, not the handiwork of humans.

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[26] Ying-Hsiu Su et al., *Human Urine Contains Small, 150 to 250 Nucleotide-sized, Soluble DNA Derived from the Circulation and May Be Useful in the Detection of Colorectal Cancer*, 6 J. Mol. Diagn. 101 (2004).

[27] F. B. J. M. Thunnissen et al., *Sputum Examination for Early Detection of Lung Cancer*, 56 J. Clin. Pathol. 805 (2003); Miep A. van der Drift, *Circulating DNA Is a Non-invasive Prognostic Factor for Survival in Non-small Cell Lung Cancer*, 68 Lung Cancer 283 (2008).

[28] Kevin A. Boynton et al., *DNA Integrity as a Potential Marker for Stool-based Detection of Colorectal Cancer*, 49 Clin. Chem. 1058 (2003).

[29] Annemarie Ziegler et al., *Circulating DNA: A New Diagnostic Gold Mine?*, 28 Cancer Treatment Rev. 255 (2002).

II. MYRIAD'S COMPOSITION-OF-MATTER CLAIMS ON ISOLATED FRAGMENTS OF GENOMIC DNA ARE INCONSISTENT WITH THIS COURT'S SECTION 101 JURISPRUDENCE BECAUSE THEY (1) ARE DIRECTED TO PRE-EXISTING PRODUCTS OF NATURE; (2) EXCLUDE OTHERS FROM OBSERVING, CHARACTERIZING OR ANALYZING THESE PRODUCTS OF NATURE BY ANY MEANS WHATSOEVER; AND (3) CREATE AN INSURMOUNTABLE BARRIER TO SCIENTIFIC PROGRESS AND TECHNOLOGICAL INNOVATION CONCERNING THESE PRODUCTS OF NATURE.

A. Composition-of-matter claims on products of Nature, such as Myriad's claims on naturally occurring DNA fragments of the human genome, are inconsistent with this Court's Section 101 Jurisprudence.

Section 101 of the Patent Act defines patentable subject matter:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful

> improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

35 U.S.C. § 101.

"The Court has long held that this provision contains an important implicit exception." *Mayo Collaborative Servs. v. Prometheus Labs*, 132 S. Ct. 1289, 1293 (2012). "Excluded from such patent protection are laws of nature, natural phenomena, and abstract ideas." *Diamond v. Diehr*, 450 U.S. 175, 185 (1981). The Court has written that "a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. . . . Such discoveries are 'manifestations of . . . nature, free to all men and reserved exclusively to none.'" *Chakrabarty*, 447 U.S. at 309 (quoting *Funk Bros.*, 333 U.S. at 130).

In *Chakrabarty*, the Court applied this rule to a human-made, genetically engineered bacterium carrying additional pieces of DNA:

> Judged in this light, respondent's microorganism plainly qualifies as patentable subject matter. His claim is not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter – a product of human ingenuity "having a distinctive name, character [and] use."

Chakrabarty, 447 U.S. at 309-10 (quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887)).

Under *Chakrabarty* and *Mayo*, is a DNA molecule related to the human genome patent-eligible? The answer depends on the nature of the DNA molecule. It is instructive to compare patent claims for three types of DNA molecule:

> *(i) recombinant DNA including human genes* – for example, a novel DNA molecule, in which a human gene has been joined to other DNA containing regulatory sequences to control its expression and enable production of therapeutic protein in a factory. (Most economically valuable patents in the biotechnology industry are of this type.)
>
> *(ii) human cDNA* – that is, a DNA molecule that is obtained by taking a "spliced" messenger RNA from a human cell and using an enzyme to "reverse transcribe" it from RNA to DNA. (These DNA sequences encode human proteins and are often used for producing proteins in factories.)
>
> *(iii) human genomic DNA* – that is, a DNA molecule whose sequence is identical to a portion of the human genome. (Myriad's claim to a monopoly on diagnostics involving the BRCA1 gene rests on claims to genomic DNA.)

In the first case, the claim is clearly to "a nonnaturally occurring manufacture or composition of matter – a product of human ingenuity." *Chakrabarty*, 447 U.S. at 309. An invention involving a human gene in this manner is clearly patent-eligible.

In the second case, the question is closer but the answer is still clear. A cDNA molecule is closely related to the RNA from which it has been reverse transcribed: in particular, it has the same "information content." But it is produced by a transformative step[30] and is a distinct chemical entity that differs from both (i) the RNA (which is a different type of nucleic acid) and (ii) the genomic DNA from which the RNA was transcribed (which contains "intervening sequences"). For this reason, the Federal Circuit concluded, unanimously and correctly, that cDNA is patent-eligible.[31]

In the third case (the one relevant to Myriad's diagnostic monopoly at hand), the arguments for patent-eligibility under Section 101 evaporate. No transformative step is involved because, as shown above, isolated DNA fragments of the human genome occur routinely in Nature.

Claims, such as Myriad's, to isolated DNA fragments of the human genome thus are not directed to "a nonnaturally occurring manufacture or composition of matter – a product of human ingenuity," but rather to a product of Nature itself. *Chakrabarty*, 447 U.S. at 309.

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[30] It can be argued that the transformative step is straightforward, but this speaks to obviousness, not patent-eligibility under Section 101.

[31] *See* 689 F.3d at 1329, 1340-41, 1348.

A discovery about genomic DNA does not involve invention of a new composition of matter, but rather is more akin to discovery of a law of Nature pertaining to a product of Nature (for example, that a pre-existing DNA sequence is associated with a high-risk of breast cancer).

B. The rationale for barring patents on a product of Nature is strongest when a patent would wall off an entire domain of Nature from study and innovation.

A major purpose behind the “important, implicit exception” concerning “‘[l]aws of Nature, natural phenomena, and abstract ideas’” is to avoid the “danger that the grant of patents . . . inhibit future innovation premised upon them.” *Mayo*, 132 S. Ct. at 1293 (citation omitted); *see id.* at 1301; *Diehr*, 450 U.S. at 185.

The Court has noted that “phenomena of nature, though just discovered, . . . are not patentable, as they are the basic tools of scientific and technological work.” *Gottschalk*, 409 U.S. at 67. In *Mayo*, this Court expanded upon *Gottschalk*, reasoning that the “monopolization of those tools through the grant of a patent might tend to impede innovation more than it would tend to promote it.” *Mayo*, 132 S. Ct. at 1293.

“The Court has repeatedly emphasized . . . [the] concern that patent law not inhibit further discovery by improperly tying up the future use of laws of nature." *Id.* at 1301. "[T]he underlying functional concern here is . . . how much future innovation is foreclosed relative to the contribution of the inventor." *Id.* at 1303.

It follows that the rationale against granting patents on the handiwork of Nature is strongest when a patent would create an insurmountable barrier to innovation.

Many patents that pertain to products of Nature do not create insurmountable barriers to innovation. For example, a monopoly on a particular method for studying a product of Nature would not preclude (and in fact might encourage) invention of an alternative method for studying the product of Nature. Similarly, a monopoly on a particular use or set of uses for a product of Nature – for example, to treat or prevent a disease – would not preclude (and in fact might encourage) development of alternative non-natural molecules that could substitute for (or improve upon) the product of Nature.

But the situation is different with respect to a composition-of-matter patent on a product of Nature (such as genomic DNA). Such a patent can be used to exclude everyone from observing, characterizing or analyzing, *by any means whatsoever*, the product of Nature. The exclusion is not limited to any particular method of analysis; it extends to all possible methods of analysis.

It is inherently impossible to circumvent this barrier. One cannot observe, characterize or analyze a product of Nature if one cannot legally possess it. A molecule is one of the "basic tools" – indeed, an *essential* tool – for studying the molecule itself. *Gottschalk*, 409 U.S. at 67. Granting a monopoly on possessing a molecule that is a product of Nature authorizes a patent holder to wall off an entire domain of Nature from observation.

Science is the systematic and cumulative study of the natural world. It generates fundamental knowledge that not only serves human curiosity but also is the intellectual fuel for practical applications, including patentable invention. For scientific progress to proceed, scientists must have the ability to study the handiwork of Nature.

To illustrate the seriousness of this issue, suppose that a monopoly had been granted on the naturally occurring human immunodeficiency virus (HIV), responsible for AIDS, or on the nucleic acid molecule that is its genome. The patent holder would have been legally entitled to use his patent to block anyone from observing, characterizing or analyzing the virus by any means whatsoever. Scientists would not have been able to rapidly learn the secrets of this insidious virus; drug developers would not have been able to develop life-saving drugs; technologists would not have been able to develop effective diagnostics; and patients would not have been able to know their HIV status. All of this progress (which saved millions of lives and led to many patentable inventions) was possible only because observation, characterization, and analysis of the product of Nature were open to all. To their credit, the discoverers of HIV obtained appropriately narrow patents that do not exclude others from observing, characterizing and analyzing naturally occurring HIV.

C. Myriad's composition-of-matter claims on genomic DNA are directed to preexisting products of Nature; exclude others from observing, characterizing or analyzing these products of Nature by any means whatsoever; and create an insurmountable barrier to scientific innovation on these products of Nature with serious consequences for medical progress and technological innovation.

The isolated DNA fragments of the human genome claimed by Myriad are products of Nature, as shown above by abundant scientific evidence.

The composition-of-matter claims to these fragments allow the patent holder to exclude others from observing, characterizing or analyzing these products of Nature by any means whatsoever.

Such claims erect an insurmountable barrier to studying these DNA sequences, with serious consequences for innovation in medicine. For example, only a *subset* of BRCA1 mutations predispose to breast cancer, while others are harmless.[32] To accurately predict a woman's risk of breast cancer, one must learn *which* mutations actually create a predisposition to the disease. This requires characterizing the BRCA1 gene in many thousands of women. Myriad's monopoly has seriously inhibited the ability of the scientific community to gather sufficient quantities of data to fully learn these laws of Nature.

III. A NARROWLY CRAFTED DECISION BY THIS COURT WOULD NOT UNDERMINE THE BIOTECHNOLOGY INDUSTRY AND INSTEAD WOULD FOSTER INNOVATION.

In the Federal Circuit's view, a decision that isolated DNA fragments are patent-ineligible would disrupt long-settled expectations and could wreak havoc on the biotechnology industry. *See* 689 F.3d at 1333, 1343-48. In fact, the Federal Circuit's concern is unfounded.

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[32] Francine Durocher et al., *Comparison of* BRCA1 *Polymorphisms, Rare Sequence Variants and/or Missense Mutations in Unaffected and Breast/Ovarian Cancer Populations*, 5 Hum. Mol. Genet. 835 (1996); Alison M. Dunning et al., *Common* BRCA1 *Variants and Susceptibility to Breast and Ovarian Cancer in the General Population*, 6 Hum. Mol. Genet. 285 (1997).

A. Most medically and commercially important biotechnology products depend on patent protection for non-naturally occurring DNA molecules, such as cDNAs and recombinant DNAs, rather than on products of Nature such as fragments of genomic DNA.

The vast majority of the medically and commercially important biotechnology products developed over the past quarter century are protected by patents on isolated DNA molecules that are *non-natural* compositions of matter, such as cDNA and recombinant DNA molecules – for such uses as artificially producing therapeutic proteins. Only a small fraction of products involve diagnostic claims to *naturally occurring* genomic DNA.

The biotechnology industry would not be substantially affected by a narrowly crafted decision holding that (1) fragments of human genomic DNA are patent-ineligible where the scientific evidence is clear that the claimed molecules themselves are routinely found in Nature and where the process for purification or synthesis[33] of such molecules is routine but (2) human cDNAs are patent-eligible, because these molecules do not occur in Nature and have clearly different functional properties from related products of Nature.[34]

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[33] If this Court does not wish to address the question of whether products of Nature are patent-ineligible under all circumstances, it can address the narrower question of whether products of Nature may be patented where their purification or synthesis is routine. As described *supra* in note 4, the physical purification of isolated DNA fragments has been routine since 1978.

B. The unfettered ability to observe, characterize and analyze the human genome will foster scientific progress and technological innovation.

Any concerns about unsettling expectations related to a limited number of diagnostic patents on human genomic DNA should be balanced against the innovation that will flow from unfettered access to this product of Nature.

Biomedicine stands on the verge of a revolution with major implications for human health. A decade ago, the scientific community completed the Human Genome Project, which revealed the complete genetic code of our species.[35] Over the past decade, stunning technological advances have reduced the cost of sequencing a human genome from billions of dollars to thousands of dollars – and it may fall in coming years to hundreds of dollars.[36] (For reference, Myriad charges approximately $3000 to sequence roughly four one-millionths of the human genome.)

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[34] *See supra* at 21.

[35] Eric S. Lander et al., *Initial Sequencing and Analysis of the Human Genome*, 409 Nature 860 (2001).

[36] Eric S. Lander, *Initial Impact of the Sequencing of the Human Genome*, 470 Nature 187 (2011).

The ability to read entire human genomes is unlocking critical secrets about cancer, diabetes, schizophrenia and many other diseases. Such studies involve identifying genetic variants associated with disease based on comprehensive genome studies of thousands of patients. These discoveries are making it possible to identify and prioritize targets for drug development, select patients for clinical trials and provide diagnostic and prognostic information.

Granting monopolies on the naturally occurring DNA of the human genome would impair the ability of patients to benefit from the fruits of this genetic revolution, by making it difficult or impossible to study the human genome as an integrated whole in scientific and medical settings. It would risk fencing off into a patchwork of private reserves the vast expanse of the human genome – one of the most remarkable "manifestations of . . . nature, [that should be] free to all men and reserved exclusively to none." *Funk Bros.*, 333 U.S. at 130.

CONCLUSION

It is well-accepted in the scientific community that isolated DNA fragments of the human genome – including isolated DNA fragments of the BRCA1 and BRCA2 genes – are found routinely in the human body and are thus patent-ineligible products of Nature. The biotechnology industry would not be substantially affected by a narrowly crafted decision here holding that (1) fragments of human genomic

DNA are patent-ineligible where the claimed molecules themselves are routinely found in Nature and where the process for purification or synthesis of such molecules is routine and (2) cDNAs are patent-eligible.

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AMICUS CURIAE BRIEF

Supreme Court, U.S.
FILED

MAR 14 2013

OFFICE OF THE CLERK

No. 12-398

In the Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF *AMICUS CURIAE* OF PROFESSOR JEFFREY A. LEFSTIN IN SUPPORT OF RESPONDENTS

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I. INTEREST OF *AMICUS CURIAE*[1]

Amicus is a Professor of Law specializing in patent law, with a particular focus on the history of patent law and its institutions. *Amicus* also holds a Ph.D. in biochemistry and molecular biology. *Amicus*'s interest in this case lies solely in furthering the development of patent law. *Amicus* submits this brief to assist this Court, in light of historical experience, in selecting the appropriate analytical framework for subject matter eligibility under 35 U.S.C. § 101.

II. SUMMARY OF ARGUMENT

In *Mayo v. Prometheus*,[2] this Court suggested, among other approaches, that claims lack patent-eligibility unless they represent inventive applications of laws of nature and natural phenomena. This analysis appears to revive the framework set forth in *Funk Brothers v. Kalo Inoculant*.[3] Historically, the *Funk* analysis was employed to invalidate a wide variety of seemingly meritorious claims, indicating the Court should proceed with caution before endorsing its analysis. Historical precedents further clarify that the test of patent-eligibility is not whether a claim implements an inventive application of a fundamental principle, but whether a claim is drawn to a fundamental principle unbounded by the patentee's mode of application. Under the latter analysis, isolated and purified DNA molecules derived from human genes are patent-eligible subject matter.

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[1] The parties have consented to the filing of this brief. Pursuant to Rule 37.6 of this Court, amicus curiae certifies that no counsel for any party authored this brief in whole or in part, that no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than amicus curiae, its members, and its counsel made such a monetary contribution to its preparation or submission.

[2] 132 S. Ct. 1289 (2012).

[3] 333 U.S. 127 (1948).

III. ARGUMENT

A. Introduction.

In *eBay v. MercExchange* the Chief Justice, quoting Justice Holmes, observed that "'a page of history is worth a volume of logic.'"[4] *Amicus*, whose research involves the history of patent law and its institutions, is prompted by the Chief Justice's observation to provide the Court with this historical perspective. In particular, given the past experience of the lower courts applying this Court's standards of subject matter eligibility, *Amicus* hopes to highlight the possible consequences of the Court's interpretation of *Mayo* in this case.

This case appears to be governed by *Mayo*, rather than by this Court's decision in *Diamond v. Chakrabarty*.[5] The issue before the Court in

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[4] 547 U.S. 388, 395 (2006) (quoting *New York Trust Co. v. Eisner*, 256 U.S. 345, 349 (1921)).

[5] 447 U.S. 303 (1980). *Amicus* notes that *Chakrabarty*'s "standard" of "distinctive name, character, and use" derives ultimately from what is now termed the "substantial transformation" test of

Chakrabarty was whether claims drawn to living organisms were patent-eligible – not whether Chakrabarty's genetically engineered bacteria were products of nature or natural phenomena. While Chakrabarty's claims were initially rejected by the Patent Office as "products of nature," that rejection was not sustained by the Patent Office Board of Appeals[6] and was not before this Court.[7] Accordingly, the precedent most relevant to this case is this Court's decision in *Mayo*.

In *Mayo* this Court appeared to set forth three possible approaches to determine whether a claim impermissibly attempts to monopolize a fundamental principle, such as an abstract idea, a law of nature, or a natural phenomenon. First, the Court indicated that a claim is not patent-eligible if it amounts to nothing more than an instruction to apply the fundamental principle.[8] Second, the Court indicated that a claim effectively pre-empting all use of a fundamental

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Customs law. *See Am. Fruit Growers v. Brogdex Co.*, 283 U.S. 1, 12-13 (1931) (looking to Customs cases to define "manufacture" as used in patent statute).

[6] *See Chakrabarty*, 447 U.S. at 306 n.3.

[7] The Court's discussion of the "product of nature" doctrine seems to have been prompted by the appellee's mention of *Funk* in his brief. The appellee had argued that if living things were not patent-eligible, this Court would have said so in *Funk*.

[8] *See Mayo*, 132 S. Ct. at 1297, 1301.

principle does not recite patent-eligible subject matter.[9] And third, the Court indicated that a claim is not patent-eligible if it represents a merely conventional or obvious application of a fundamental principle, adding nothing more than routine and well-understood steps to the underlying discovery.[10]

It is the last aspect of *Mayo* that prompts this brief. If *Mayo* is read to deny patent-eligibility where the claimed subject matter is obvious once the underlying natural law or natural phenomenon has been discovered, then this Court will have revived the framework set forth in 1948 by *Funk*. The manner in which the Circuit Courts of Appeal applied that framework in the 20 years following *Funk* suggests that this Court should be hesitant before endorsing that course. Rather, *Mayo*'s first aspect – a rejection of claims that amount to no more than a directive to apply a law of nature or a natural phenomenon – is the one most consistent with the historical precedents that *Mayo* itself invoked. The Court should apply that framework to the present case.

B. The Requirement for an Inventive Application of a Law of Nature Revives the Analytical Framework of *Funk*.

Funk concerned claims to a mixture of bacteria that promoted nitrogen fixation in leguminous plants.

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[9] *See id.* at 1302. However, *Mayo* suggested that preemption *per se* is not the test for excluded subject matter. *See id.* at 1303.

[10] *See id.* at 1294, 1298.

Because each strain of bacteria was specific to a particular crop, a farmer planting multiple crops needed to apply multiple bacteria to his fields. However, different strains of bacteria tended to inhibit each other's activity, requiring the farmer to purchase and apply a separate inoculant to each crop. The patentee in *Funk* had discovered that particular strains of bacteria would not inhibit each other's activity when mixed together. He therefore disclosed, and claimed, a mixed inoculant of nitrogen-fixing bacteria selected for their mutual non-inhibitory qualities.[11]

This Court concluded that the patentee had not claimed an invention or discovery within the meaning of the patent statutes. The Court regarded the patentee's discovery of mutual non-inhibition as the discovery of a basic phenomenon of nature:

> Discovery of the fact that certain strains of each species of these bacteria can be mixed without harmful effect to the properties of either is a discovery of their qualities of non-inhibition. It is no more than the discovery of some of the handiwork of nature and hence is not patentable.[12]

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[11] Justice Frankfurter regarded the claims as unpatentable not because they were drawn to products of nature, but because the patentee had not provided sufficient disclosure to support claims encompassing all non-inhibitory mixtures of bacteria. *See* 333 U.S. at 133-34.

[12] *Id.* at 131.

The Court conceded that the patentee's discovery may have been "ingenious."[13] But patentability, in the Court's view, was predicated on the ingenuity in the application, not the ingenuity of the discovery. The patentee's application of the newly discovered principle was the production of a mixed culture. Once the patentee's discovery had been made, the application in the form of a mixed culture was well within the ordinary skill in the art:

> But once nature's secret of the non-inhibitive quality of certain strains of the species of Rhizobium was discovered, the state of the art made the production of a mixed inoculant a simple step. . . . That is to say, there is no invention here unless the discovery that certain strains of the several species of these bacteria are non-inhibitive and may thus be safely mixed is invention. But we cannot so hold without allowing a patent to issue on one of the ancient secrets of nature now disclosed. All that remains, therefore, are advantages of the mixed inoculants themselves. They are not enough.[14]

Thus, under the *Funk* analysis, the patentee's discovery of a new law of nature or natural phenomenon was immaterial. What mattered was whether the patentee's application of that scientific discovery was inventive. To put it in the language of *Mayo*, given the natural phenomenon of non-inhibition, the patentee's application in the form of a mixed inoculant was nothing more than "well-understood, routine, conventional activity" already engaged in by workers in the field.[15]

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[13] *Id.*

[14] *Id.* at 132.

If *Mayo* is to be understood as a requirement that a patentee's application of a law of nature or a natural phenomenon embody something more than the conventional or obvious, then it is difficult to distinguish *Mayo*'s analytical framework from *Funk*'s. To the contrary, in *Mayo* this Court grounded its requirement for an "inventive concept" beyond the law of nature in *Parker v. Flook*;[16] *Flook*, in turn, based its analysis on *Funk*.[17] Accordingly, if this Court interprets *Mayo* as denying patent-eligibility to a claim unless the claim embodies a non-obvious *application* of a scientific discovery, then this Court will have revived the analysis set forth in *Funk*.

The *Funk* analysis would appear to deny patent-eligibility of the claims challenged in this case.[18] The claims in dispute are generally drawn to polynucleotides encoding *BRCA* polypeptides – a definition broad enough to encompass either isolated and purified genomic sequences, or isolated and purified cDNAs. Under the *Funk* analysis, the "natural phenomenon" discovered by the patentee appears to be the natural sequence of the *BRCA* loci. Once one eliminates the discovery in this case – the identification and sequencing of the *BRCA* loci – there is no apparent inventive application that would satisfy the *Funk* analysis. The application of that discovery – the purification and separation of the claimed DNA molecules from their natural contexts[19] – appears to have been obvious, given the routine nature of DNA manipulation at the time of invention.[20] But regardless of whether the claims in this case would pass muster under *Funk*, the historical experience of *Funk*'s analysis indicates that this Court should not endorse

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[15] 132 S. Ct. at 1298.

[16] *See id.* at 1294 (citing *Parker v. Flook*, 437 U.S. 584, 593 (1978), for requirement of "inventive concept").

[17] *Flook*, 437 U.S. at 591 ("*Mackay Radio* and *Funk Bros.* point to the proper analysis for this case: The process itself, not merely the mathematical algorithm, must be new and useful.").

[18] One might superficially distinguish *Mayo* from the present case on the grounds that *Mayo* concerned process claims, as compared to the compositions of matter at issue here. However, the claims in *Funk* were drawn to compositions of matter, and *Mayo* itself draws no distinction between categories of potentially patent-

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eligible subject matter. Moreover, this Court has made clear that the reasoning of *Funk* is equally applicable to product and process claims. *See Gottschalk v. Benson*, 409 U.S. 63, 67-68 (1972).

[19] There is no distinction between genomic DNA and cDNA under this analysis. While cDNA represent a species not found in nature, the processing and removal of intervening sequences in mRNA is performed by the cell itself. The human intervention – reverse transcription to cDNA – was entirely conventional at the time of the invention.

[20] One peculiar consequence of the "inventive application" analysis is that patent-eligibility appears to depend on the time the invention was made. What is routine and conventional now was revolutionary in the past. But the question of whether a claim is drawn to nothing more than a fundamental principle ought not to depend on the state of the art at the time.

an "inventive application" interpretation of *Mayo* in this case.

C. Historical Application of the *Funk* Framework Illustrates the Risks of the Inventive Application Doctrine.

Prior to the creation of the Federal Circuit, the Circuit Courts of Appeal implemented *Funk*'s principle that a claim based on a newly discovered law of nature or natural phenomenon was not patentable, unless the patentee had added something more than conventional or obvious activity to the underlying principle. The range of seemingly meritorious claims that were invalidated for lack of an inventive application of a natural law should give this Court pause before it endorses that test in the present case.[21]

Two years after *Funk*, the Seventh Circuit applied *Funk*'s analysis in *Davison Chemical Corp. v. Joliet Chemicals, Inc.*[22] *Davison Chemical* dealt with a process for producing silica gel. While the process for making silica gel was known in the art, the patentee had discovered that the temperature of the wash step determined the size of the gel's pores. He therefore claimed an improved process wherein the temperature of the wash step was adjusted to control the density of the final product.

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[21] The District Courts have begun applying the *Mayo* framework to question the validity of claims based on discovery of a new natural phenomenon. *See, e.g.*, *Aria Diagnostics, Inc. v. Sequenom, Inc.*, No. C11-06391, 2012 WL 2599340, at *11-12 (N.D. Cal. July 5, 2012) (method of rapidly diagnosing fetal genetic abnormalities based on presence of cell-free fetal DNA in the maternal bloodstream); *Tessenderlo Kerley, Inc. v. Or-Cal, Inc.*, No. C11-04100, 2012 WL 2054994, at *5-6 (N.D. Cal. June 5, 2012) (method of treating crops with calcined kaolin based on discovery that particulates increase carbon dioxide absorption).

[22] 179 F.2d 793 (7th Cir. 1950).

But the Seventh Circuit regarded the relationship between wash temperature and pore size as a "newly discovered scientific fact."[23] Under *Funk*, it was necessary that the patentee's *application* of that fact be inventive. According to the court, once the relationship between temperature and pore size had been discovered by the patentee, the application in the form of the improved process was merely conventional and routine activity:

> [W]e assume that Connolly [the inventor] discovered that the temperature of the wash water determined the pore size and, therefore, the specific gravity or density of the gel but, we think, that, once having discovered this, it required nothing more than the ordinary skill of the scientist to determine that maintaining the temperature of the water at a constant point would make the size of the pore, and the density of the silica gel, uniform.[24]

The Seventh Circuit therefore held the patent invalid.

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[23] *Id.* at 794.

[24] *Id.* at 795.

The Court of Customs and Patent Appeals (CCPA) followed *Davison Chemical* in *In re Arnold*,[25] involving a claim to a process of electrostatic welding. The process of heating materials by alternating electrostatic fields was known. But the patent applicant discovered that molecules near the surface of a material responded more readily than interior molecules to alternating electrostatic fields.[26] By choosing a particular frequency based on the response of surface molecules, the applicant could selectively weld the surface of the material, or selectively weld a plasticizer applied to the surface.[27]

But according to the CCPA, the discovery that surface molecules had a different anomalous dispersion range compared to the interior molecules was a "phenomenon of nature" that had been discovered by the applicant.[28] The patentee's application – choosing a frequency that would selectively weld the surface molecules – was merely the result of his discovery. The claims accordingly lacked "invention" under *Funk*.[29]

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[25] 185 F.2d 686 (C.C.P.A. 1950).

[26] The basis for this effect was said to be the difference in anomalous dispersion range of a dipolar substance between the interior and surface molecules. *See id.* at 691.

[27] *See id.* at 688.

[28] *See id.* at 691.

[29] *See id.* Arnold did eventually succeed in patenting other claims from the same application. *See* U.S. Patent No. 2,575,251.

National Lead Co. v. Western Lead Products Co.[30] was similar to *Davison Chemical*. In a process for making a lead/lead oxide suspension (useful for storage batteries), the patentee had supposedly discovered that two different crystalline forms of lead oxide were present.[31] The patentee further claimed to have discovered that the temperature of the reaction determined the relative proportions of the two crystalline forms of lead oxide. By regulating the temperature of the reaction, the patentee could control the proportion of these two forms and thereby the uniformity of the final product. The patentee therefore claimed an improved process, in which the temperature of the reaction was held within particular ranges by regulating the rate of influx of molten lead.[32]

However, even assuming that the patentee had been the first to discover these phenomena, the Ninth Circuit held the process not patentable under *Funk*. The relationship between reaction temperature and product uniformity was considered to be a scientific fact or law of nature; the question was whether the patentee's application of that law was inventive.[33]

> Our inquiry must therefore focus upon whether an artisan, knowing that the temperature of the reaction determines the uniformity of the

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[30] 324 F.2d 539 (9th Cir. 1963).

[31] *See id.* at 541.

[32] *See id.* at 540.

[33] *See id.* at 542.

> product, would require more than ordinary skill to discover the process of controlling the reaction temperature by varying the feed of molten lead into the [prior art] Barton pot.[[34]]

Since the patentee used only conventional methods to regulate the temperature of the reaction, the method of performing the reaction at an optimized temperature was unpatentable.

Perhaps the most extreme example of this line of authority was the Third Circuit's decision in *Armour Pharmaceutical Co. v. Richardson-Merrell, Inc.*[35] The patentee made the surprising discovery that trypsin – a proteolytic enzyme with anti-inflammatory properties – could be absorbed by the small intestine and thereafter transported into the bloodstream.[36] The prior art had administered trypsin to patients via injection or other cumbersome methods. But in light of the small intestine's ability to absorb the enzyme, the patentee determined that oral administration would be possible if the trypsin was given a coating permitting it to resist digestion in the stomach and reach the small intestine intact.[37] The patentee therefore claimed a composition of trypsin given an enteric coating for use in the treatment of inflammation.[38]

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[34] *Id.*

[35] 396 F.2d 70 (3d Cir. 1968).

[36] *See id.* at 71-72. The discovery was unexpected, due to the large size of the trypsin molecule and the fact that the human body already secretes these enzymes into the digestion system.

[37] *See id.* at 72.

Though the Third Circuit regarded the patentee's invention as precisely the sort of discovery the patent laws ought to protect,[39] the court felt bound by *Funk* to invalidate the claim. The ability of the small intestine to absorb trypsin and similar enzymes was a natural phenomenon. Under *Funk*, the test for patentability was whether anything more than ordinary skill would be necessary to reach the patentee's application of that discovery. The answer was no:

> Once nature's secret that the ileum would absorb trypsin was uncovered, any artisan would have known the process of enterically coating the trypsin to enable it to pass through the acidic environment of the stomach and continue into the ileum.[40]

And even if the patentee's discovery was the anti-inflammatory effect of trypsin administered to the small intestine, not merely the ability of the small intestine to absorb trypsin, the application of that newly discovered principle still lacked inventiveness under *Funk*.[41]

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[38] *See id.* at 71 n.3.

[39] *See id.* at 73: "Thus, it would seem that allowing a patent on the restricted use Martin made of his discovery of a natural phenomenon would not only be consistent with our patent laws, but would further their purpose. The employment of the newly discovered principle of nature would remain open to all those desiring to utilize it. We discern no requirement in the policy of the patent law that the method by which the discovery be utilized also be a new method. However, the Supreme Court and several courts of appeal have held to the contrary." (Footnote omitted.)

[40] *Id.* at 74.

The claims in *Funk*, and in the *Davison Chemical* line as well, were invalidated for "lack of invention" – which, prior to the 1952 Patent Act, was a term encompassing the requirement defined as obviousness under 35 U.S.C. § 103.[42] Although *Funk* has been occasionally dismissed as a case about obviousness,[43] neither *Funk* nor the *Davison Chemical* line is an obviousness case. In neither of these cases would the claims have been obvious in the modern sense, because the patentee's discovery was not in the prior art. It was only upon the patentee's discovery of a "law of nature" that one of ordinary skill would have had reason to employ the conventional instrumentalities at issue in each case.

D. The Modern Foundation of the Inventive Application Test Rests on a Misapprehension of Historical Precedent.

While *Funk* first articulated the requirement that a claim must embody a non-obvious application of a natural law, this Court's modern cases have grounded this principle on the Court of Exchequer's 1841 opinion in *Neilson v. Harford*,[44] which was also considered in *O'Reilly v. Morse*[45] and *Tilghman v. Proctor*.[46]

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[41] *See id.* at 75.

[42] *Funk* and *Davison Chemical* were decided prior to the 1952 Patent Act, while *National Lead* and *Armour Pharmaceutical* were decided after.

[43] The Federal Circuit dismissed *Funk* on these grounds in the present case.

The patent in *Neilson* concerned the application of heated air to improve the performance of blast furnaces. On the question of whether Neilson had attempted to patent the abstract principle of applying heated air to the smelting process, or machinery embodying that principle, Baron Parke stated:

> We think the case must be considered as if the principle being well known, the plaintiff had first invented a mode of applying it by a mechanical apparatus to furnaces; and his invention then consists in this—by interposing a receptacle for heated air between the blowing apparatus and the furnace.[47]

Flook took this language to indicate that a fundamental principle underlying an invention should be regarded as part of the prior art, with a further "inventive concept" necessary to secure a patent.[48] Likewise, *Mayo* suggested that the patent in *Neilson* was sustained because the patentee had applied unconventional steps to confine the claims to a particular useful application.[49] Unfortunately, *Flook* and *Mayo* relied on a mistaken interpretation of *Neilson*.

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[44] Webster's Patent Cases 295 (1841).

[45] 56 U.S. 62 (1853).

[46] 102 U.S. 707 (1880).

[47] Webster's Patent Cases at 371.

[48] *Flook*, 437 U.S. at 592, 594.

In *Neilson*, the Court of Exchequer did not condition patentability on an inventive application of a natural law. What guided the Court of Exchequer was the distinction between patenting an abstract principle divorced from any mode of applying it for practical use, and patenting a new mode of applying a principle toa particular practical use. The same distinction should guide this Court in this case.

The issue of patentability in *Neilson* was sufficiency of disclosure: whether the patentee had sufficiently disclosed his method of heating air prior to introduction into the furnace.[50] The defendants charged that the patentee had failed to describe the invention such that one of ordinary skill in the art could carry out the invention[51] – an argument that today would be phrased as lack of enablement under 35 U.S.C. § 112. For example, the patent did not disclose the shape and size of the heating vessel, nor how one of ordinary skill in the art could scale up the process from the small forges that Neilson had employed.[52]

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[49] *Mayo*, 132 S. Ct. at 1300.

[50] Though the defendant's plea in *Neilson* included the defense that the patent was void "as being for a principle," Webster's Patent Cases at 296, the defendant's argument was focused almost entirely on insufficiency of disclosure. The defendant's motion for a new trial was grounded on this issue, as well as alleged errors in the specification and discordance between the patent's specification and title. *See id.* at 330. According to the defendants, the inventor did not even understand the principle behind his invention. *See id.* at 344 ("It has been said that Mr. Neilson was not aware of the nature and principle of his discovery.").

Ultimately, the patent was sustained not because Neilson's apparatus was inventive, but because it was *largely conventional*. Both the patentee and the court emphasized that the heating of air and the apparatus Neilson employed were well known in the art.[53] Neilson discovered the effect of heating air before its introduction into the furnace and disclosed a mode for heating air in its passage from the blowing apparatus to the furnace. Because the heating of air in various kinds of vessels was routine and conventional in the art, one of ordinary skill in the art could readily devise other machinery achieving the same end.[54] The patent was therefore not invalid for lack of sufficient disclosure.

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[51] *See, e.g., id.* at 307-09 (defendant's argument that disclosure did not enable practice of the invention).

[52] *See id.* at 339.

[53] *See id.* at 337 (interposition of Baron Alderson); *id.* at 344 (patentee's argument: "The mode of heating air was perfectly well known; it was no discovery of Mr. Neilson's, every body knew it.").

[54] *See id.* at 372 (patentee proved to jury that "competent workman" could vary the shape of the air vessel to achieve desired effect).

Contemporary opinions not only underscore this understanding of *Neilson*, but in fact refute the interpretation suggested in *Mayo* and *Flook*. As discussed by this Court in *Risdon Iron & Locomotive Works v. Medart*[55] and *Tilghman*,[56] the Court of Session considered the same patent in Scottish infringement proceedings shortly after *Neilson*.[57] Lord Justice Hope instructed the jury on the distinction between an unpatentable "abstract philosophical principle"[58] (such as a law of nature or property of matter) and a patentable application of that principle to practical ends. But that distinction was *not* based on whether the patentee's application of that fundamental principle was in itself inventive:

> The main merit, the most important part of the invention, may consist in the conception of the original idea—in the *discovery of the principle in science, or of the law of nature*, stated in the patent, and *little or no pains may have been taken in working out the best manner and mode of the application of the principle* to the purpose set forth in the patent.[59]

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[55] 158 U.S. 68, 73 (1895).

[56] 102 U.S. at 725.

[57] *Househill Coal & Iron Co. v. Neilson*, Webster's Patent Cases 673 (1843).

[58] *Id.* at 683.

[59] *Id.* (emphasis added). "It would be very strange and unjust," added Justice Hope, to deny patentability to the application of a

In other words, patentability did not depend on whether the patentee's practical application added something beyond the conventional and obvious to an underlying law of nature or a natural phenomenon.[60]

This understanding of *Neilson* – that one may not patent a fundamental principle in the abstract, divorced from its mode of application – was the understanding relied on by this Court in *Morse*. Morse was not denied his eighth claim because his application of the newly discovered "galvanic current" was merely conventional or routine.[61] It was because he invented only a particular mechanism, not a universal means for electromagnetic communication.[62] *Morse*, like *Neilson*, was a case about patent scope: given the state of the art, was the patentee's disclosure sufficient to enable application of the principle embodied in his mode of

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principle on the grounds that the inventor had discovered the principle as well as its practical application. *Id.* at 684.

[60] Justice Hope's instructions were affirmed by the House of Lords on appeal, but an error on the question of abandonment required a new trial. *See id.* at 708-17 (overruling defendant's exceptions based on specification, but granting new trial on the question of prior public use).

[61] Quite the opposite: the Court noted that Morse's application depended on "certain complicated and delicate machinery, adjusted and arranged upon philosophical principles, and prepared by the highest mechanical skill." *Morse*, 56 U.S. at 117.

[62] *Id.* ("But Professor Morse has not discovered, that the electric or galvanic current will always print at a distance, no matter what may be the form of the machinery or mechanical contrivances through which it passes.").

application? In both *Neilson* and *Tilghman* the answer was yes: the patentee had invented a mode of application of a natural principle, and his patent extended to other applications in that same mode. In *Morse* the answer was clearly no: Morse was entitled to claim his mode of application of the electromagnetic force, but not the universal use of the electromagnetic principle for communication at a distance.

That long-standing distinction[63] – between a claim directed to a fundamental principle in the abstract and a claim directed to a particular mode of application of a fundamental principle – is what should guide the Court in this case.[64] This Court should make clear that *Mayo* denied patent-eligibility to the claimed process not because it was obvious in light of the underlying discovery, but because it amounted to nothing more than a directive to apply a natural law. It therefore attempted to monopolize a law of nature in the abstract, unbounded by a mode of applying that law to a particular practical use.

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[63] *See also* 1 William C. Robinson, *The Law of Patents* § 137, 141 (1890) (distinguishing between "principle" as unpatentable natural physical force and "principle" as inventor's idea of operative means applied to practical effect).

[64] This distinction is consistent with *Flook*, which dealt not with a newly discovered law of nature or natural phenomenon, but with an abstract idea. This Court also emphasized the unpatentability of abstractions in *Bilski v. Kappos*, 130 S. Ct. 3218 (2010).

IV. CONCLUSION

In this case the Court should reject an interpretation of *Mayo* that would revive the "inventive application" analysis of *Funk*. Instead, the Court should endorse an interpretation of *Mayo* that denies patent-eligibility to claims that do nothing more than direct the application of a natural law without reference to a specific mode of application.

The claims at issue in this case are drawn to particular isolated and purified DNA molecules: synthetic derivatives of natural genes. Unlike the claims in *Mayo*, they do not represent abstract fundamental principles, unbounded by the patentee's mode of application. This Court should therefore affirm the judgment of the Federal Circuit, and hold that claims to isolated and purified DNA molecules derived from human genes are not invalid for lack of patent-eligibility under 35 U.S.C. § 101.

Respectfully submitted,

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AMICUS CURIAE BRIEF

Supreme Court, U.S.
FILED
MAR 14 2013
OFFICE OF THE CLERK

No. 12-398

In The
Supreme Court of the United States

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THE ASSOCIATION FOR
MOLECULAR PATHOLOGY, ET AL.,

Petitioners,

v.

MYRIAD GENETICS, INC., ET AL.,

Respondents.

◆

**On Writ of Certiorari to the
United States Court of Appeals
for the Federal Circuit**

◆

BRIEF FOR *AMICUS CURIAE* LYNCH SYNDROME INTERNATIONAL IN SUPPORT OF RESPONDENTS

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INTEREST OF *AMICUS CURIAE*[1]

Amicus Lynch Syndrome International ("LSI") is an all-volunteer organization founded and governed by Lynch syndrome survivors, their families, and health care professionals who treat Lynch syndrome. LSI funds research and educates the general public and health care professionals about Lynch syndrome. By enhancing survivability, LSI creates hope and positively impacts thousands of lives worldwide.

Lynch syndrome is an inherited genetic disorder. Relative to the general population, people with Lynch syndrome have a greatly increased risk of developing one or more fatal cancers by early middle age. Lynch syndrome cancers tend to be more aggressive and do not have the extended "dwell time" of other cancers. Genetic screening can, in many cases, confirm whether an individual has Lynch syndrome. Because carriers of Lynch syndrome prematurely develop aggressive cancers, an individual with a confirmed diagnosis of Lynch syndrome can be monitored aggressively so that cancer development is caught early, when treatment is most effective. Readily available, reliable, approved, and comprehensive genetic testing is thus of the highest import for individuals with Lynch syndrome.

---

[1] Counsel for all parties have consented to the filing of this brief, and their consents have been lodged with the Clerk of this Court. No counsel for any party had any role in authoring this brief, and no person other than the named *amicus* and its counsel has made any monetary contribution to the preparation and submission of this brief. *See* Rule 37.

As new Lynch genes and gene variants are discovered, it is imperative that tests be developed to identify them. If such tests are not developed, some Lynch syndrome patients will not be diagnosed early – or at all – and will not be monitored aggressively. Consequently, Lynch syndrome cancers that otherwise could have been caught and effectively treated at an early stage will be inadequately diagnosed and treated, resulting in unnecessary suffering and untimely death for these patients.

Genetic tests for these new and variant genes will be created and commercialized either by next generation start-up biotechnology companies or by existing diagnostic companies. Next generation start-up biotechnology companies need venture capital funding to exist, but venture capitalists will not provide funding unless the technology that the start-ups are developing can be patented and protected from copyists. Similarly, larger companies will not invest the money required to produce a reliable test unless they can be assured of a return on their investment by way of protection from copyists. This protection can be provided by method-of-use patents and kit patents, and need not necessarily come from composition-of-matter claims such as claim 1 of Myriad's U.S. Patent No. 5,837,492. However, an overly broad approach to the claims before this Court could inadvertently and adversely impact method-of-use patents and kit patents.

Thus, *amicus* LSI has a strong interest in ensuring that any holding by the Court is narrowly crafted, does not restrict method-of-use or kit patents, and thus does not foreclose patent eligibility for future genetic tests, including future Lynch syndrome genetic tests.[2] Specifically, any holding of the Court should be limited to the issue at hand, *i.e.*, whether claims to human genes recite a composition of matter patent-eligible under 35 U.S.C. § 101.

◆

SUMMARY OF ARGUMENT

Genetic tests should remain patent-eligible to the broadest extent possible. The broad scope of patent-eligible subject matter under 35 U.S.C. § 101 is well-established. Moreover, the development, approval, and commercialization of new genetic tests are made possible primarily by patent eligibility. Indeed, as new Lynch syndrome genes and gene variants are discovered, new tests to detect such genes and variants must be developed: The earlier patients with those genetic markers can be diagnosed, the sooner they can receive the more aggressive monitoring that will prolong their lives. The information provided by genetic testing not only enhances survivability but also permits intelligent decision-making concerning the right to procreate and have a family.

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[2] As explained more fully *infra* in Point III, the references herein to patents for "genetic tests" include patents for the use of particular molecules, including DNA molecules, in such tests.

The development and commercialization of genetic tests require significant amounts of capital, but capital sources will not provide the necessary funding unless the newly developed tests will have patent protection. Only patent protection will assure the capital sources of a sufficient investment return to make the provision of funding worthwhile.

Accordingly, any holding of the Court should be limited to the issue of whether claims to human genes recite a composition of matter patent-eligible under 35 U.S.C. § 101 and should neither restrict method-of-use or kit patents nor foreclose patent eligibility for future genetic tests, including future Lynch syndrome genetic tests.

◆

ARGUMENT

I. Genetic Tests Should Remain Patent-Eligible to the Broadest Extent Allowed by Law

The Constitution provides Congress with the power to "promote the Progress of Science and the useful Arts, by securing for limited Times to . . . Inventors the exclusive Right to their respective . . . Discoveries." U.S. Const. art. I, § 8, cl. 8. To that end, Congress established the broad ambit of patent-eligible subject matter in 35 U.S.C. § 101: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."

This Court has noted the breadth of patent-eligible subject matter: "In choosing such expansive terms . . . modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope." *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010) (citation omitted). "Congress took this permissive approach to patent eligibility to ensure that 'ingenuity should receive a liberal encouragement.'" *Id.* at 3225 (citations omitted). Genetic tests have fallen squarely within the four corners of Section 101 for over a decade, as evidenced by the average yearly entry of 3,482 U.S. patents and patent applications into the DNA Patent Database for the period 1996-2011.[3]

Insofar as Section 101 also sets forth a "utility requirement,"[4] no one argues that genetic tests are not useful. Indeed, many arguments for denying patent eligibility to Myriad's claims paradoxically rely on the utility of genetic testing, as evidenced by an unmet demand for genetic testing driven by underlying economic factors.[5]

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[3] *DNA Patent Database*, available at http://dnapatents.georgetown.edu/.

[4] *See*, *e.g.*, U.S. Patent and Trademark Office, Guidelines for Examination of Applications for Compliance with Utility Requirement, available at http://www.uspto.gov/web/offices/pac/mpep/s2107.html (referring to "utility requirements of 35 U.S.C. 101 and 112").

This reliance is not surprising because genetic testing, if reliable and comprehensive, can provide life-changing information.[6] In contrast, inaccurate genetic testing can result in "misdiagnosis, inappropriate and/or delayed treatment, anxiety and in rare cases, even death."[7]

Lynch syndrome provides an example of an unmet need for accurate, approved, reliable, readily available, and comprehensive genetic testing. New Lynch syndrome genes, and new variants of existing Lynch syndrome genes, continue to be discovered.[8] Such testing for these new and variant Lynch syndrome genes would be life-changing and likely will come about only if genetic testing remains patent-eligible.

In sum, the breadth of Section 101, the urgent unmet need for new genetic tests, and the fact that development and commercialization of new genetic tests are made possible primarily by patent eligibility make it imperative that genetic testing remain patent-eligible.

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[5] *See* U.S. Dept. of Health & Human Servs., *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests: Report of the Secretary's Advisory Committee on Genetics, Health, and Society* (Apr. 2010).

[6] *See* Kathy L. Hudson *et al.*, *Oversight of US genetic testing laboratories*, 24 Nature Biotechnology 1083 (2006) ("*Hudson*").

[7] *Hudson* at 1089.

[8] *See Genetic Testing*, available at http://www.lynchcancers.com/index.php/genetic-testing.

II. If Genetic Tests Are Held Patent-Ineligible, Unnecessary Patient Suffering and Untimely Patient Death Will Result

Many genetic disorders disproportionately and adversely impact small subsections of the population. One such disorder is Lynch syndrome, which is also known as hereditary nonpolyposis colon cancer. Colon cancer is the third most common cancer diagnosed in men and women, with 101,340 new cases diagnosed annually.[9] Colon cancer causes about 50,000 deaths annually – approximately 9% of all cancer deaths.[10] Up to 80% of Lynch syndrome individuals will develop colorectal cancer, with an average onset age of 42 years (versus 70 years for non-inherited colorectal cancer).[11] Table 1 below presents the lifetime risk of cancer development in patients with Lynch syndrome versus the general population.[12]

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[9] American Cancer Society, *Cancer Facts & Figures 2011* ("*Cancer Facts*"), at 12.

[10] *Cancer Facts* at 12.

[11] Vincent W. Yang, M.D., Ph.D., *Population-Based Screening and Cascade Testing for Lynch Syndrome: Are We There Yet?* Presentation at Medicine Grand Rounds, Loyola University Medical Center, Mar. 27, 2012 ("*Yang*"), slides 11-12.

[12] *Yang*, slide 12.

Table 1. Lifetime cancer risk: Lynch syndrome versus general population.[13]

Type of Cancer	**Persons with Lynch syndrome (%)**	**General Population (%)**
Colorectal	80-85	5-6
Endometrial	64-71	2-3
Ovarian	20	1-2
Gastric	13	1
Kidney	12	1
Bladder	8-12	1-3
Brain	4	0.6
Pancreatic	~3.7	~0.5
Bile Duct	2	0.6
Small Bowel	1-4	0.01

Recent studies also suggest increased risk for cancers of the prostate and breast when Lynch syndrome is present.[14]

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[13] For Lynch-related pancreatic cancer data in Table 1, *see* Fay Kastrinos *et al.*, *Risk of Pancreatic Cancer in Families With Lynch Syndrome*, 302 J. Am. Med. Ass'n 1790 (2009). For Lynch-related endometrial and kidney cancer data in Table 1, *see* Markku Aarnio, *Clinicopathological Features and Management of Cancers in Lynch Syndrome*, 2012 Patholog. Res. Int. 350309 (2012). For Lynch-related ovarian cancer data in Table 1, *see* Cleveland Clinic Genomic Medicine Institute, *Lynch Syndrome*, available at http://my.clevelandclinic.org/Documents/genomics/Lynch%20Sydrome_Fact%20Sheet.pdf. For Lynch-related bladder cancer data in Table 1, *see* R.S. van der Post *et al.*, *Risk of urothelial bladder cancer in Lynch syndrome is increased, in particular among MSH2 mutation carriers*, 47 J. Med. Genet. 464 (2010).

[14] *See* C.M. Bauer *et al.*, *Hereditary prostate cancer as a feature of Lynch syndrome*, 10 Fam. Cancer 37 (2011); M.D. Walsh

(Continued on following page)

Lynch syndrome is inherited. The form of inheritance is known as autosomal dominant inheritance, meaning that a child need only receive a defective gene from one parent to inherit Lynch syndrome.[16]

Lynch syndrome genes increase cancer risk by inhibiting repair of mistakes made in genetic replication. "Variations in the *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes increase the risk of developing Lynch syndrome. All of these genes are involved in the repair of mistakes . . . [in] DNA replication."[16] Mutations in any of these genes may prevent proper repair of DNA replication mistakes, leading to development of cancer. Because Lynch syndrome mutations affect both men and women, the defective repair genes are more important, in terms of clinical significance, than the genes for breast cancer susceptibility, BRCA1 and BRCA2.

Genetic testing is crucial for individuals with Lynch syndrome and their families. "A positive result for Lynch syndrome (HNPCC) makes one a 'mutation carrier' and . . . serves as verification of having an increased risk of cancer."[17] Because of the early onset, increased frequency, and aggressiveness of cancers associated with Lynch syndrome, persons diagnosed

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et al., *Lynch Syndrome-Associated Breast Cancers: Clinicopathologic Characteristics of a Case Series from the Colon Cancer Family Registry*, 16 Clin. Cancer. Res. 2214 (2010).

[15] *Yang*, slide 11.

[16] *Lynch Syndrome*, available at http://ghr.nlm.nih.gov/condition/lynch-syndrome.

[17] *Genetic Testing*.

with Lynch syndrome are given elevated cancer monitoring and surveillance. "Regular screening examinations . . . can result in . . . the diagnosis of cancers at an early stage, when they are most treatable."[18] Through preventive measures like early diagnosis and surveillance, "enhanced quality of life and longevity can be achieved and individuals and families can be protected from cancer."[19]

If genetic tests are not developed for new Lynch syndrome genes and for new variants of known Lynch syndrome genes, some Lynch syndrome patients will not be diagnosed early and hence will not be given elevated cancer monitoring and surveillance. Aggressive Lynch syndrome cancers that otherwise could have been caught and effectively treated at an early stage will go undiagnosed and untreated, resulting in unnecessary suffering and untimely death for these patients.

Genetic tests for these new and variant genes are likely to be created and commercialized either by next-generation start-up biotechnology companies or by existing, larger diagnostic companies. As discussed more fully *infra* in Point III, next-generation start-up biotechnology companies need venture capital funding to exist, but venture capitalists will not provide funding unless the technology being developed by such companies can be patented. Similarly, large companies will direct their research and development efforts elsewhere if a copyist is immediately able to reproduce a genetic test without the research and development required to create the first test on the market.

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[18] *Cancer Facts* at 1.

[19] *Lynch Syndrome International*, available at http://www.lynchcancers.com/.

In particular, the commercialization of new genetic tests depends on their underlying patent eligibility. For example, Myriad's BRCA1/2 test was initially developed at a university with federal grant research money. However, it was patent protection for the test that led venture capitalists to invest in Myriad, with the result that the test is now publicly available. Moreover, the patents at issue expire in the next few years. Accordingly, the system worked properly: A company received a financial incentive for commercializing the test; obtained, and will soon use up, a period of time in which it has an exclusive right to make the test; and, as a result, the test is now widely obtainable. Upon expiration of the patents, the test will soon become even more widely obtainable, and the cost at which the test is made will likely drop as competitors enter the market. Moreover, the tests are heavily regulated both in the United States and abroad. While Lynch syndrome victims are hoping to have the same type of new tests available, an unnecessarily broad holding by this Court here could inadvertently dash those hopes by relegating victims to potentially unregulated one-off tests of doubtful accessibility.

The Court has long acknowledged that "the rights and welfare of the community must be fairly dealt with and effectually guarded" in the patent system. *Kendall v. Winsor*, 62 U.S. 322, 329 (1858). "A patent by its very nature is affected with a public interest. As recognized by the Constitution, it is a special privilege designed to serve the public purpose of promoting the 'Progress of Science and useful Arts.'" *Precision Instrument Mfg. Co. v. Auto. Maint. Mach. Co.*, 324 U.S. 806, 816 (1945) (quoting U.S. Const. art. I, § 8, cl. 8).

New genetic tests are urgently needed and will serve the public interest. Such tests obviate unnecessary patient suffering and reduce untimely patient death.

For all of these reasons, patent eligibility for future genetic tests, including future Lynch syndrome genetic tests, must not be foreclosed.

III. Patent Eligibility Determines Whether Life-Changing Genetic Tests Will Be Developed, Approved, and Commercialized

A. Patents are the basis for the biotechnology industry

Patents are *the* basis for the biotechnology industry. Patents "give rise to the innovation that results in the creation of [genetic] diagnostics and treatment options based thereon . . . ."[20] Should this Court hold

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[20] Suzannah Sundby and Eric Mirabel, *No One Is Patenting Your Genes: The Ripple Effect if Isolated DNA Claims Are Made*

(Continued on following page)

invalid any of Myriad's composition-of-matter claims to DNA fragments, it should be careful not to limit the ability of innovators to patent *uses* of such DNA fragments, as well as kits employing such fragments and other diagnostic innovations that lie beyond the grant of *certiorari*.

B. Venture capitalists will not fund start-ups whose technology cannot be patented

"[W]ithout patent protection for Biotech inventions, no one would be willing to make the substantial investment required to research, develop and bring . . . small market products through the multi-year FDA approval process."[21] Because Lynch syndrome occurs in approximately 1 in 1,000 live births,[22] the percentage of Lynch syndrome carriers in the general population is relatively small. Lynch syndrome carriers therefore cannot provide a "mass market" for genetic diagnostics.

Patent Ineligible, IP Watchdog, Dec. 14, 2012, available at http://www.ipwatchdog.com/2012/12/14/no-one-is-patenting-your-genes-the-ripple-effect-of-isolated-dna-claims-are-made-patent-ineligible/id=31437/ (*"Ripple Effect"*).

[21] *Ripple Effect*.

[22] *Yang*, slide 11; *cf.* H. Hampel *et al.*, *The Search for Unaffected Individuals with Lynch Syndrome: Do the Ends Justify the Means?* 4 Cancer Prev. Res. 1 (2011) (estimating that up to 1 in 370 individuals may have Lynch syndrome).

Patents provide much needed protection and incentive to develop new genetic diagnostic assays in such small markets, including new Lynch syndrome genetic diagnostic assays. Absent patent protection, these new assays "will likely go the way of treatments and medicines for orphan diseases prior to the 1983 Orphan Drug Act . . . ."[23] No "patents for isolated DNA and diagnostics means 'one size fits all' as the investment in R&D will only be made for what can be sold for the masses. Say 'goodbye' to personalized medicine."[24] "Personalized medicine" involves tailoring therapeutics for individual patients through diagnostic tests for genetic mutations known as biomarkers. Such therapeutic tailoring is essential for the survival of Lynch syndrome families. In the words of one Lynch syndrome cancer survivor: "Without personalized medicine, entire families have and will continue to be wiped out."[25]

Venture capitalized companies, including biotechnology companies, are inherently at risk of failure. The risk exists regardless of the definition of failure. "If failure means liquidating all assets, with investors losing all their money, an estimated 30% to

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[23] *Ripple Effect*.

[24] *Ripple Effect*.

[25] For a personal oral history of a family devastated by Lynch syndrome cancers, *see Workshop 6: Cancer Genetics* – Judi Ruggiero-Reed, available at http://www.youtube.com/watch?v=rw7OCX9otsw ("*Ruggiero-Reed*").

40% of high potential U.S. start-ups fail . . . ."[26] "If failure is defined as failing to see the projected return on investment . . . then more than 95% of start-ups fail . . . ."[27] Approximately 75% of "venture-backed firms in the U.S. don't return investors' capital."[28] In view of these long odds, Myriad's survival, due largely to patent-eligibility for its genetic tests, has been a miracle for BRCA1 and BRCA2 patients: Without Myriad, it is possible that only fragmented and potentially unregulated testing would be available. Lynch syndrome patients desperately need access to the quality testing that Myriad has been able to provide to BRCA1 and BRCA2 patients.

Investment in biotechnology companies, especially in start-up genetic diagnostic companies, is even riskier because such investment is long-term. In "the decade since the initial sequencing of the human genome, other anticipated advances – such as the rise of genetics based personalized medicine – have yet to take off."[29] "It takes much longer than you'd like to believe when you make the first investment."[30] Indeed,

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[26] Deborah Gage, *The Venture Capital Secret: 3 Out of 4 Start-Ups Fail*, The Wall Street Journal, Sept. 19, 2012, available at http://online.wsj.com/article/SB10000872396390443720204578004980476429190.html (*"Venture Capital Secret"*).

[27] *Venture Capital Secret*.

[28] *Venture Capital Secret*.

[29] Joanna Glasner, *The Gene Scene*, Venture Capital Journal, Feb. 25, 2013.

[30] *The Gene Scene* (quoting Bill Ericson, managing director of Mohr Davidow Ventures).

"the genetics-based diagnostics space seems to be an area where there's more venture capital going in than being returned to investors."[31] Long-term financial risks associated with funding biotechnology companies, and the small market for many genetic diagnostic tests, make the availability of patent protection a mandatory prerequisite to the development of such tests.

C. Academia is no substitute for the biotechnology industry

If diagnostic genetic testing were held patent-ineligible, academia could not assume the biotechnology industry's key role in developing next-generation diagnostic tests. Academia might still continue such research, but is unlikely to "spend, more appropriately risk, millions to conduct the additional R&D to take that basic research and make a product available to the public so that one can have medical treatment that is personalized for that person[.]"[32] Federal budgetary constraints make this scenario even more unlikely: "With the current budget constraints on our Federal Government, it's not likely that we'll see additional Federal research grants for universities to conduct basic research that results in potential products, *e.g.*, diagnostic tests, which are essential for personalized medicine."[33] At present, there is no hope of expanded government funding for academic research sufficient to allow academic researchers to expend the capital needed to produce a regulated, high-quality, broadly available test.

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[31] *The Gene Scene.*

[32] *Ripple Effect.*

Any ruling by this Court that diminishes or casts doubt upon the patent eligibility of genetic diagnostic testing risks killing the goose (the biotechnology industry) that lays the golden eggs (*e.g.*, genetic diagnostic testing). In this case, one of the golden eggs could be a test to help Lynch syndrome victims avoid or better treat cancer.

IV. Allowing Genetic Tests to Remain Patent-Eligible Will Allow Patients to Make Informed, Intelligent Decisions Concerning the Exercise of Constitutional Rights Previously Affirmed by This Court

Courts have not significantly appreciated the positive impact that diagnostic genetic testing has on individual constitutional rights, and the negative impact that a decision rendering diagnostic genetic tests patent-ineligible would have on such rights.

Individual constitutional rights include, but are not limited to, the right of privacy of married persons including access to contraception; the power of parents to control the education of their children; and family sanctity. *See, e.g.*, *Griswold v. Connecticut*, 381 U.S. 479 (1965); *Moore v. East Cleveland*, 431 U.S. 494 (1977); *Zablocki v. Redhail*, 434 U.S. 374 (1978).

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[33] *Ripple Effect.*

The life-changing information provided by diagnostic genetic tests allows patients to make informed, individual decisions regarding the exercise of their constitutional rights. Using Lynch syndrome as an example, genetic diagnostic testing can help individuals intelligently decide whether to form a family; whom to form a family with; whether or not to have children; whether or not to adopt in lieu of naturally conceiving children; and whether and how long to use contraception. Moreover, absent genetic testing, Lynch syndrome parents cannot properly prepare or educate their children regarding how to survive and to navigate the health-care system.

Foreclosure of patent eligibility for future genetic tests would result in failure to develop new genetic tests. Thus, some individuals would not be able to ascertain their genetic carrier status for conditions such as Lynch syndrome. Should this Court issue a decision that renders genetic testing patent-ineligible, the Court would be consigning a vulnerable minority of individuals to an ignorance of their genetic status that would meaningfully impede the exercise of their constitutional rights. It would also allow Lynch syndrome to continue to devastate families across generations.[34]

◆

CONCLUSION

Because of the importance of genetic testing to the Lynch syndrome community and because of the importance of patent eligibility to the developers of new genetic tests, LSI urges the Court to issue a narrow holding that does not foreclose future patents on genetic testing.

Respectfully submitted,

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[34] *Ruggiero-Reed*.

AMICUS CURIAE BRIEF

RECORD
AND
BRIEFS

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MAR 14 2013
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No. 12-398

In the
Supreme Court of the United States

ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,

Petitioners,

v.

MYRIAD GENETICS, INC., ET AL.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

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INTEREST OF *AMICUS CURIAE*[1]

Amicus Curiae MPEG LA, LLC is a leading packager of patent pools and other one-stop non-exclusive patent licensing solutions offering wide access to important technologies. Its programs include Librassay®, which licenses on a non-exclusive basis nearly 400 patents to isolated human deoxyribonucleic acid (DNA) molecules, biomarkers, diagnostic assays, and other medical technologies. The patents belong to research institution leaders such as Johns Hopkins University, Ludwig Institute for Cancer Research, Memorial Sloan-Kettering Cancer Center, National Institutes of Health (NIH), Partners HealthCare, The Board of Trustees of the Leland Stanford Junior University, The Trustees of the University of Pennsylvania, University of California, San Francisco and the Wisconsin Alumni Research Foundation.

SUMMARY OF ARGUMENT

Contrary to petitioners' absolutist position, Congress did not categorically exclude scientifically isolated DNA molecules from patentable subject matter under 35 U.S.C. § 101. Nor are the competing policy concerns irreconcilable. The life-changing inventions at issue are exactly the kinds of inventions the patent system ought to reward, as respondents' brief explains. But the incentive provided by the patent system to develop biotechnologies need not hinder other important research or uses, as petitioners claim. Real-world experience in other cutting-edge industries has shown that the availability of non-exclusive licenses through patent licensing programs like Librassay strikes an effective balance.

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[1] The parties' written consents to the filing of this brief are on file with the clerk. No counsel for a party authored this brief in whole or in part, and no person other than MPEG LA paid for or made a monetary contribution toward the preparation and submission of this brief. The views expressed in this brief are MPEG LA's alone. MPEG LA does not speak for participants in its patent licensing programs.

I. Unlike the processes this Court held to be unpatentable in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), this case concerns concrete, and man-made, compositions of matter. The patented strands are different from naturally occurring DNA in important, substantive ways. Those differences are the very reasons why the patented molecules are so beneficial, so inventive, and so costly to develop.

II. Petitioners and others have posited a false dichotomy between providing incentives to innovate through patents, on the one hand, and permitting researchers and health care professionals to make use of others' patented inventions, on the other. MPEG LA solved similar problems during the advent of the digital-video age by assembling and offering a patent pool providing nonexclusive access under a single license to many patents owned by many patent holders. That model—which enabled inventors to recover their investments in patented technologies while also enabling others to use the inventions—has become a template for cutting through so-called patent thickets in many different technological disciplines. As detailed below, that history is already repeating itself in this context, where Librassay has formed a one-stop, non-exclusive, market-driven license affording convenient access to the kinds of patents at issue here.

Even if market mechanisms did not resolve all of the legitimate policy concerns, Congress or the courts could employ more tailored approaches to balancing patent rights with other interests. The competing policies can be reasonably balanced under the existing patent system—unless petitioners have their way and this Court takes a sledgehammer to the entire enterprise of isolated DNA research and product development.

ARGUMENT

I. SCIENTIFICALLY ISOLATED DNA MOLECULES ARE ELIGIBLE FOR PATENT PROTECTION BECAUSE THEY ARE SUBSTANTIVELY DIFFERENT FROM ANYTHING FOUND IN NATURE

Petitioners argue that patents on isolated human DNA impermissibly claim "abstract ideas." Pet. Br. 17, 26 (citing *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012)). In contrast to the method at issue in *Mayo*, however, these patents cover specific compositions of matter. *See Ass'n for Molecular Pathology v. USPTO*, 689 F.3d 1303, 1325 (Fed. Cir. 2012) (Opinion of Lourie, J.). Compositions of matter are concrete. And they are eligible for patent protection so long as they are man-made: While "a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter," "a nonnaturally occurring manufacture or composition of matter"—that is, "a product of human ingenuity having a distinctive name, character and use"—is patentable subject matter. *Diamond v. Chakrabarty*, 447 U.S. 303, 309–10 (1980) (internal quotation marks and brackets omitted); *see also Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948).

The human DNA found in nature is present in the form of 46 chromosomes, each of which contains a single, large undifferentiated DNA-containing construct. *See Ass'n for Molecular Pathology*, 689 F.3d at 1313. In contrast, isolated strands of specific DNA molecules with specific functions "are not found in nature. They are obtained in the laboratory and are man-made, the product of human ingenuity." *Id.* at 1325.

Petitioners contend that "adding the word 'isolated'" to the patent claims is merely "clever draftsmanship," because "[i]solated DNA does not have markedly different characteristics from any found in nature." Pet. Br. 27. While "isolated" is a word, it is one that conveys an important, substantive difference. Resp. Br. 51–53. Even without wading deeply into the science, there are at least three clear indications that the differences between the claimed molecules and naturally occurring DNA are substantively important.

First, far from being immaterial, the differences are the very reasons why the isolated molecules are useful in scientific, medical, and research applications. The isolated molecules are used "to 'probe' for target DNA in a patient sample or to 'prime' the production of copies of the target DNA in the laboratory." Resp. Br. 7. These functions are possible only because of the way the lab-created, isolated molecules react with naturally occurring DNA. *Id.* at 7–8. Only by providing an isolated, exogenously manufactured, and specific DNA molecule can a specific target DNA sequence embedded in the entire human genome be identified. *Id. at* 8 & n.3.

Second, the claimed compositions are the "product of human ingenuity." *Chakrabarty*, 447 U.S. at 309–10. Successfully isolating DNA molecules involves difficult scientific judgments about "how to define the beginning and end of the[] genes" and how to separate those genes from larger DNA molecules—judgments that are nothing if not "inventive." Resp. Br. 6–7.

Third, while not dispositive in itself, the enormous cost required to isolate and develop the claimed molecules is telling. *See, e.g.*, *id.* at 5. If the claimed molecules were not materially different from naturally occurring DNA molecules, they would not be so difficult or costly to come by.

II. THE MARKET IS SOLVING ANY PURPORTED POLICY PROBLEMS

Petitioners posit a false dichotomy between providing an incentive for innovation and allowing the public to use the resulting inventions in further scientific and medical research and product innovation. As MPEG LA's own experience shows, the availability of patent pool and other one-stop non-exclusive licenses can resolve that concern. The whole point of the patent system is to *balance* these interests across a wide spectrum of fields of human endeavor. *See Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 63 (1998). Petitioners would annihilate that balance in one of the areas where it is needed most.

A. Respondents' Inventions Are Among Those Most Deserving Of Patent Protection

The reasons for providing patent protection are at their zenith here. Successfully isolated DNA molecules provide enormous benefits for society, leading to new cures for diseases, new diagnostic technologies that enable health care providers to detect and treat illnesses, and new tools that enable researchers to discover therapies and diagnostics for the future. Insulin, human growth hormone, and erythropoietin are just three of the many recombinantly produced human protein therapies made using isolated DNA molecules. *See* Courtney J. Miller, *Patent Law and Human Genomics*, 26 Cap. U. L. Rev. 893, 900 (1997). Petitioners themselves recognize the benefits of isolated DNA molecules, as their own policy arguments depend on them. *See* Pet. Br. 41–42.

But without some means for those who develop isolated DNA molecules to recoup their substantial investments, these important inventions may never come to be. Under our Constitution and Patent Act, the patent system provides that means, and "motivate[s] invention," by granting exclusive rights for a limited time. *Pfaff*, 525 U.S. at 63. As Abraham Lincoln explained, patents add "the fuel of interest to the fire of genius, in the discovery and production of new and useful things." Abraham

Lincoln, Second Lecture on Discoveries and Inventions (Feb. 11, 1859), *in* 3 THE COLLECTED WORKS OF ABRAHAM LINCOLN 356, 363 (Roy P. Basler, ed., 1953). That incentive is especially important in contexts like this, where the costs and investment risks required to develop breakthrough inventions that advance the health sciences and grow the American economy are enormous.

Moreover, denial of patent protection could be counter-productive even from the limited standpoint of promoting public access to others' existing inventions. It could force inventors to keep their discoveries confidential, in hopes of relying on trade secret protections. That would undermine the patent system's fundamental objective of encouraging "public disclosure of new and useful advances in technology." *Pfaff*, 525 U.S. at 63. It also would provide an insufficient incentive for invention, because "trade secret law provides far weaker protection in many respects than the patent law." *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 155 (1989) (brackets and internal quotation marks omitted).

B. MPEG LA's Experience Shows that Non-Exclusive Licensing Solutions Are Capable of Addressing Petitioners' Policy Concerns

Patent pool and other one-stop non-exclusive licensing solutions can address the policy concerns raised by petitioners. In the 1990s, for example, as video technology was transitioning to digital media, product and content developers faced a problem. Technology in the form of the MPEG-2 videocompression standard was available to bring high-resolution digital video into consumer products, but hundreds of patents owned by many patent holders threatened its implementation.

Following a review by the U.S. Department of Justice, MPEG LA offered the first modern patent pool providing nonexclusive access under a single license to many patents owned by many patent holders. DOJ explained that the MPEG-2 pool was "likely to provide significant cost savings to [l]icensors and licensees alike, substantially reducing the time and expense that would otherwise be required to disseminate the rights to each MPEG-2 Essential Patent to each would-be licensee." Letter from Joel I. Klein, Asst. Att'y Gen., Dep't of Justice, to Garrard R. Beeney, Sullivan & Cromwell LLP (June 26, 1997), *available at* http://www.usdoj.gov/atr/public/busreview/215742.htm.

By making MPEG-2 video widely available, the patent pool enabled an explosion of innovative new products for delivering digital video to consumers, including televisions, DVD and Blu-ray Disc players, personal computers, video discs, digital cable boxes, satellite TV receivers, cameras, and game devices. The vast majority of these products are licensed by nearly 2,000 companies through MPEG LA's patent pool.

MPEG LA's model has become the pro-competitive template for many different technologies. Today, MPEG LA operates licensing programs consisting of some 8,000 patents in 74 countries featuring more than 160 patent holders and some 5,500 licensees.

Just as the MPEG-2 platform ushered in a new era for digital video, the Human Genome Project enabled a new era of genetic diagnostics and personalized medicine. And today's genetic researchers and product developers face some of the same patent-related problems that the 1990s' digital-video developers faced: the need to obtain access to essential patent rights while also respecting the need to compensate inventors for their significant investments and contributions. To address these problems, MPEG LA launched Librassay in September 2012. *See* Librassay Press Release, September 27, 2012, *available at* https://www.librassay.com/Media.aspx; News Flash, *Gene Patent Pool Set to Launch*, 155 Am. J. Med. Genetics x (2011), *available at* http://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.34380/pdf; Lawrence A. Horn, *The MPEG LA Licensing Model: What Problem Does It Solve in Biopharma and Genetics?*, *in* GENE PATENTS AND COLLABORATIVE LICENSING MODELS 33–41 (G. Van Overwalle, ed., 2009); Lawrence A. Horn, *Alternative Approaches to IP Management: One-stop Technology Platform Licensing*, 9 J. Comm. Biotech. 119 (2003).

Librassay balances the interests of all concerned by making patent rights for genetic diagnostics and research tools available to anyone who wishes them on reasonable, affordable, and non-discriminatory non-exclusive licensing terms. By joining Librassay, patent holders grant MPEG LA the right to sublicense. The patents are made searchable using key words and placed into general categories for online browsing, free of charge. *See* http://www.librassay.com. Sublicensees sign a standard agreement providing a royalty-free license for basic research and education-related uses, and a royalty-bearing license for commercial products and tests. MPEG LA collects the royalties and distributes them to patent holders according to set formulas, while retaining a portion of the royalties as an administrative fee.

Presently, the facility contains nearly 400 patents including claims to isolated DNA molecules and other biomarkers. The patents come from research institution leaders such as Johns Hopkins University, Ludwig Institute for Cancer Research, Memorial Sloan-Kettering Cancer Center, NIH, Partners HealthCare, The Board of Trustees of the Leland Stanford Junior University, The Trustees of the University of Pennsylvania, University of California, San Francisco and the Wisconsin Alumni Research Foundation.

Librassay will thereby speed the development and commercialization of new diagnostic tests and products. By aggregating complementary patents under one roof, Librassay also allows licensees to license multiple patent rights from many different patent holders at an "anti-stacking" royalty rate, which is the same for all licensees and is likely lower than a licensee could negotiate on its own in a series of bilateral negotiations. At the same time it offers patent owners the opportunity for wider adoption of their technologies, reasonable compensation for their research investments and the incentive to invest more. This aggregation also provides value to patent holders with patents whose value can be realized principally in conjunction with other pieces of a larger diagnostic puzzle.

If MPEG LA's experience with consumer-electronics pools is any indication, outlying patent holders will join as Librassay becomes the established way of doing business.[2] More and more patent holders in the diagnostics field understand that nonexclusive licensing is viable. For example, NIH recommends that, "[w]henever possible, non-exclusive licensing should be pursued as a best practice." Nat'l Institutes of Health, *Best Practices for the Licensing of Genomic Inventions: Final Notice*, 70 Fed. Reg. 18413, 18415 (Apr. 11, 2005); *see also, e.g.*, Org. for Econ. Dev. and Co-operation, *Guidelines for the Licensing of Genetic Inventions* § 5.3 (2006) ("License agreements relating to foundational genetic inventions should generally be non-exclusive to encourage broad access for researchers and patients and broad use of the genetic invention."), *available at* http://www.oecd.org/sti/biotech/36198812.pdf.

"Before making any changes that could serve to undermine the time-tested structure for stimulating investment in innovation, market-driven approaches including patent pools or patent clearinghouses and/or incentives to stimulate non-exclusive licensing . . . should continue to be explored . . . ." Frances Toneguzzo, *Editoral: Impact of Gene Patents on the Development of Molecular Diagnostics*, 5 Expert Opinion on Med. Diagnostics 273, 275 (2011).

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[2] MPEG LA's MPEG-2 patent pool started with eight patent holders and 100 patents and grew to include 27 patent holders with more than 1,000 patents worldwide.

Especially considering that the marketplace is already moving toward this solution, removing all patent incentives for these important inventions would be a wholly disproportionate and unbalanced response.

C. Other Finely Tuned Solutions Are Available To Address Any Remaining Issues

Of course, no patent holder is required to include its patent in a facility like Librassay. And in some instances, an exclusive license may be necessary to recoup particularly high development costs. *See* 70 Fed. Reg. at 18415. In any case the market should be given every opportunity to work within the existing system. Even if non-exclusive license pools do not always provide a solution, they greatly ameliorate the concerns raised by petitioners. And other, less drastic remedies can solve any remaining problems.

If market mechanisms do not develop adequately, Congress could consider enacting a finely tuned legislative package to balance appropriately the various interests at stake, as it has before. *See* Gregory P. Lekovic, *Genetic Diagnosis and Intellectual Property Rights: A Proposal to Amend "The Physician Immunity Statute"*, 4 Yale J. Health Pol'y L. & Ethics 275, 278 (2004); *see also, e.g.*, 35 U.S.C. § 287(c) (providing that "medical practitioner[s]" and "related health care entit[ies]" are generally immune from awards of damages, injunctive relief, and attorneys' fees for claims arising out of surgical procedures); 35 U.S.C. § 271(e) (immunizing a limited category of medical research related to Food and Drug Administration regulatory processes from infringement liability).

If problems persisted, courts might consider exercising their "equitable discretion . . . consistent with traditional principles of equity." *eBay v. MercExchange LLC*, 547 U.S. 388, 394 (2006). For example, a court might, in an appropriate case, consider both the conduct of the patent holder and the public's need for access to a particular technology in determining whether to grant an injunction against infringement. Equity allows courts to proceed on "a case-by-case basis . . . with awareness of the fact that specific circumstances, often hard to predict in advance, could warrant special treatment in an appropriate case." *Holland v. Florida*, 130 S. Ct. 2549, 2563 (2010) (internal quotation marks omitted).

Allowing the market to work, supplemented if necessary by tailored legislative or judicial action, remains the correct approach. Throwing the baby out with the bathwater is not.

CONCLUSION

The Court should hold that isolated human DNA molecules are patent-eligible subject matter.

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March 14, 2013

AMICUS
CURIAE
BRIEF

RECORD
AND
BRIEFS

No. 12-398

[illegible]
FILED
[illegible] 31 [illegible]

In The
Supreme Court of the United States

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THE ASSOCIATION FOR
MOLECULAR PATHOLOGY, ET AL.,

Petitioners,

v.

MYRIAD GENETICS, INC., ET AL.,

Respondents.

◆

**On Writ Of Certiorari To The
United States Court Of Appeals
For The Federal Circuit**

◆

BRIEF OF KALI N. MURRAY AND ERIKA R. GEORGE AS *AMICI CURIAE* IN SUPPORT OF PETITIONERS

◆

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INTEREST OF *AMICI CURIAE*

Kali N. Murray is an assistant professor of law at Marquette University Law School.[1] Before teaching at Marquette, she practiced law at Venable, LLP, where she focused on patent litigation. Drawing upon her experience as a litigator, she teaches courses in patent law, international intellectual property, and property law. She has concentrated her academic research agenda on the varied players enforcing, governing, and participating in patent law, whether citizens, businesses, or the USPTO as an administrative agency.

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[1] Petitioners gave their blanket consent for *amici* to file briefs on October 3, 2012. Respondents have consented to the filing of this brief on January 28, 2013. No counsel representing any party to the case authored this brief in whole or in part, and no counsel or party made any monetary contribution to the preparation or submission of the brief.

Institutional affiliation is provided for informational purposes only.

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SUMMARY OF THE ARGUMENT

The public's interest in the constitutional patent system is varied. An individual patent, like an invalid statute, can impose significant harm on a range of social interests. Among these social harms may be the communicative barriers imposed on the physician-patient relationship, the communicative barriers placed on researchers who seek to use the relevant information contained within a patent, and the communicative barriers placed on advocates who seek to ensure public health by disseminating information to impacted communities. The United States Court of Appeals for the Federal Circuit ("Federal Circuit"), therefore, erred below by failing to address these social harms.

Myriad's patents in human genes and related methods fail the constitutional prerequisite of invention. An authoritative testing of the validity of these patents under the common law exceptions to Section 101 of the Patent Act of 1952 is necessary to end the injury imposed upon individual and organizational plaintiffs who find that their ability to give and receive information under the First Amendment has been improperly impeded. Further, the injuries emanating from Myriad's patents violate the dignity interests embodied in the Thirteenth Amendment.

We respectfully urge the Court to recognize that Myriad's patents currently violate a number of constitutional rights, injuring both individual and organizational plaintiffs, and, for this reason, should be invalidated.

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ARGUMENT

I. PATENTS ON HUMAN GENES ARE NOT INVENTIONS PROTECTED BY PATENT LAW.

A. Art. I, § 8, Clause 8 of the United States Constitution Mandates that Invention is a Constitutional Prerequisite for Patent Protection.

Article I, Section 8, Clause 8 grants to Congress the power to "promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." U.S. Const. Art. I, § 8, cl. 8. This constitutional grant creates a parallel equivalence: it protects Authors in their Writings and protects Inventors in their Discoveries. *Eldred v. Ashcroft*, 537 U.S. 186, 223 (2003) ("[T]he grant of exclusive rights to their writings and discoveries is intended to encourage the creativity of "Authors and Inventors.") (Stevens, J., dissenting). Where "the *sine qua non* of copyright is originality," the *sine qua non* of patent is invention. *Feist Pubs. Inc. v. Rural Tel. Serv. Co., Inc.*, 499 U.S. 340, 345 (1990). Aptly summarized, "[i]nvention – both for patent eligibility *and* for patentability – thus require[s] *creativity in the application* of scientific discoveries; that is, more than merely applying the discoveries to a new use, as reflected in the particular machinery or method steps described and claimed in the patent." Joshua D. Sarnoff, *Patent-Eligible Inventions After* Bilski: *History and Theory*, 63 HASTINGS L.J. 53, 69 (2011) (emphasis in original) (citing Giles S. Rich, *Principles of Patentability*, 28 GEO. WASH. L. REV. 393, 393-94 (1960)).

The requirement of invention serves the same purpose as its textual equivalent, "originality" in copyright law, that is, ensuring a basic level of independent creation by the inventor. *Compare Feist*, 499 U.S. at 345 ("Original, as the term is used in copyright, means only that the work was independently created by the author (as opposed to copied from other works), and that it possesses at least some minimal degree of creativity") *with* William Callahan Robinson, *A Treatise on the Law of Patents* 103 (1890) ("An invention is the result of an inventive act."). The requirement of invention in patent law, though – unlike that of copyright – requires more than a minimum degree of creativity and – unlike that of copyright – has been the subject of statutory clarification in § 103 of the Patent Act of 1952. Section 103 requires that an inventor demonstrate an objective claim to a creative act by demonstrating that the invention was non-obvious based on a series of objective factors, including the scope and content of the prior art, the person having ordinary skill in the art, and the differences between the prior art and the claimed invention. The existence of more specific codification, under § 103, of *what* level of creativity is required, does not mean that the separate invention inquiry under the common law exclusion principle has been eliminated. Rather, it suggests that the question should be focused on assessing whether an inventive act is an independent creation of the inventor.

The constitutional prerequisite of invention, therefore, serves to explain its embodiment in statutory and common law content of patent law. Statutory recognition of this prerequisite has been included in some form since § 1 of the Patent Act of 1790 granted invention to those who had "invented or discovered" patentable subject-matter. Patent Act of 1790, ch. 7, § 1 (1790); *see also* Patent Act of 1836, ch. 357, 5 Stat. 117 (July 4, 1836); Patent Act of 1870, ch. 230, 16 Stat. 198-217 (July 8, 1870); Patent Act of 1952, Pub. L. No. 82-593, 66 Stat. 792.[2] The separate statutory

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[2] The separate requirement of invention embodied in the terms "invents or discovers" should also not be conflated with the separate clause that defines the categories of patentable subject-matter. These basic categories of subject-matter reflects another constitutional requirement which restrict patents to those that are "useful arts." Chisum summarizes that "[t]he general purpose of the statutory classes of subject matter is to limit patent protection to the field of applied technology . . . 'the

(Continued on following page)

requirement embodied in § 101 has often been conflated with § 103. These requirements are not the same. Section 101 requires that an invention originates with the inventor. The question of *what level* of creativity is embodied in § 103. Section 103 replaces what had often been a difficult inquiry into the inventor's state of mind at the time of invention. *See McClain v. Ortmayer*, 141 U.S. 419, 427 (1891) ("[T]he truth is, the word [invention] cannot be defined in such manner as to afford any substantial aid in determining whether a particular device involves an exercise of the inventive faculty."); *Graham v. John Deere Co. of Kansas City*, 86 S. Ct. 684, 691 (1966). As this Court has recognized, conflating these two requirements will create significant legal uncertainty in the application of these principles. *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289, 1304 (2012).

Likewise, the exclusionary principles embodied by the common law also embody the constitutional prerequisite of invention by suggesting "laws of nature, physical phenomena, and abstract ideas" are not patentable. *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010) (quoting *Diamond v. Chakrabarty*, 447

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useful arts.'" 1 *Chisum on Patents* 6-7 (2010) (citing U.S. Const. Art. I, § 8, cl. 8). Since inception, the term "useful arts" essentially meant "helpful or valuable trades." Edward C. Waltersheid, *To Promote the Progress of Useful Arts: American Patent Law and Administration*, 1798-1836, 51 (1998) (defining what the term meant in 1797).

U.S. 303, 309 (1980)) (internal quotation marks omitted). These common law exceptions then both specify "when an eligible 'invention' has been created within the statutory classes of things and process enumerated in section 101," Sarnoff, *supra* at 93, as well as "reflect the *absence* of fulfillment of the critical statutory requirement of section 101 that a person 'invents or discovers' one of the specified classes of subject matter, and are not exceptions to those classes of subject matter." *Id.* (emphasis in original).

These exclusionary principles suggest that ours is a constitutional system with dual objectives. Our constitutional patent regime seeks not only to incentivize the creative activity of a patent claimant but also to protect the preconditions for creative activity by preserving certain types of information such as the laws of nature, physical phenomena and abstract ideas from aggressive claims that would serve to block access to these basic building blocks of scientific inquiry and information exchange. *See infra* at 14. As this Court recognized in *Eldred v. Ashcroft*, 537 U.S. at 217, the communicative impact of a patent differs in kind from a copyright, as a patent represents a "monopoly of expression" that differs in kind from a copyright. A "copyright gives the holder no monopoly on any knowledge" while the grant of a patent prevents the "full use by others of the inventor's knowledge." *Id.* Thus, the constitutional prerequisite of invention as embodied in Section 101, and the exclusionary principle embodied in the common law exceptions, serve to ameliorate the expressive harms that may result from a grant of an undue "monopoly of expression" to an improvidently granted patent. In this, they serve as "built-in First Amendment accommodations." *Golan v. Holder*, 132 S. Ct. 873, 890 (2012).[3] Thus, the common law exceptions to patentable subject matter are analogous to the idea-expression dichotomy, 17 U.S.C. § 102(b) (2006), and the fair-use exception within patent law, § 107, which provide similar protection within copyright law of First Amendment values.

B. Patents in Human Genes and Related Claim Methods Do Not Require a Basic Level of Creativity and Therefore are Not Inventions within the Statutory and Common Law Meaning of Invention.

Patents should not be granted to human genes because genes – much like the factual compilations at issue in *Feist* – do not owe their origin to an act of inventorship. 499 U.S. at 345. No one truly "invents" natural occurrences or scientific principles. *E.g., In re Norris*, 179 F.2d 970, 972 (C.C.P.A. 1950); *Reynolds v. Emaus*, 87 F. Supp. 451, 453 (W.D. Mich. 1949). "This

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[3] The existence of such "built-in" accommodations may not, however, preclude a direct constitutional harm that may arise from the existence of an improvidently granted patent, *see infra*, Section II. An improvidently granted patent, may like an poorly drafted statute, create such significant constitutional harm to such a wide range of plaintiffs, that further remedies may be had beyond the scope of the statutory patent regime.

Court, however, has recognized that too broad an interpretation of this exclusionary principle could eviscerate patent law." *Mayo Collaborative Services*, 132 S. Ct. at 1293. "[A]ll inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas." *Id.* The constitutional question, as embodied in its statutory and common law forms, then, is how to distinguish between a non-protected natural occurrence, abstract ideas, or scientific principle, and a patented invention. *See id.*

The answer is a simple one: in order to assess whether an invention should be accorded the relevant patent protection, a basic inquiry must be made whether the invention originates with the inventor. U.S. Const. Art. I, § 8, cl. 8 (granting "to . . . Inventors the exclusive Right to *their*. . . . *Discoveries*.") (emphasis added). Patentable inventions originate with inventors; invention is the result of *their* inventive act. The contours of this test are suggested by this Court's analysis in *Feist*, 499 U.S. at 347. In *Feist*, this Court stated that factual information was not original because a fact's origin does not stem from the acts of any one author. *Id.* ("The first person to find and report a particular fact has not created the fact; he or she has merely discovered its existence."). The existence of information that has been discovered does not reside with the discoverer. *Id.* Rather, the information existed before it was discovered and for that reason, the information is not original. The distinction Justice O'Connor draws is "one between creation and discovery." *Id.* This Court has concluded that facts, including scientific ones, are not original and therefore do not warrant copyright protection. *Id.* at 347-48, 350.

Myriad's "discovery" of the BRCA gene was mere discovery of already existing facts; thus, the claims in the human gene did not originate with Myriad. *See Feist*, 499 U.S. at 347. Myriad has failed to demonstrate at all that the origins of its improvidently granted patent resulted from independent creation. Myriad did not locate the human gene at issue. Rather, Dr. Mary-Claire King led a team of researchers to initially map the human gene at issue (and did not receive a patent for this "discovery" of a naturally occurring process). *See* Jeff M. Hall et al., Linkage of Early-Onset Familial Breast Cancer to Chromosome 17q21, 250 SCIENCE 1684 (1990).[4] Myriad did not invent a new sequencing technique to identify the nucleotide order of BRCA genes; Myriad merely applied known sequencing techniques to identify the nucleotide order of BRCA genes. *See Ass'n for*

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[4] *See also* Shobita Parthasasrathy, *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care*, 185-86 (2007) ("British scientists, health-care professionals, and activists asserted that even if genes were inventions that could be patented and owned, discovering the BRCA genes entailed a collective effort involving researchers, women, and funding bodies in Britain as well as the United States . . . Some geneticists pointed out that Myriad's claims to sole ownership were particularly offensive because most Britons . . . credited Mike Stratton, not Myriad, with finding the BRCA2 gene.")

Molecular Pathology v. U.S. Patent and Trademark Office, 653 F.3d 1329, 1373 (2011).

Myriad's claim to an inventive act is its *isolation* of the human gene. The inventiveness of this claim is unpersuasive. An inventive act within the context of a naturally occurring material requires a marked change in functionality of the purified substance in order to sustain a claim of patentability. *In re Merz*, 97 F.2d 599, 601 (1938) (holding that there was no right to a patent on a purer version of ultramarine, but recognizing that if a claimed article is "of such purity that it differs not only in degree but in kind it may be patentable"); *see also In re King*, 107 F.2d 618, 620 (C.C.P.A. 1939) (same, for purified vitamin C); *In re Marden*, 47 F.2d 958, 959 (C.C.P.A. 1931) (same, for purified vanadium); *Gen. Elec. Co. v. DeForest Radio Co.*, 28 F.2d 641, 643 (3d Cir. 1928) (same, for purified tungsten). A demonstration of an inventive act within natural substances is only sustainable if the "purification" results in a product with such distinct characteristics that it becomes "for every practical purpose a new thing commercially and therapeutically." *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95, 103 (C.C.S.D. N.Y. 1911); *see also Merck & Co. v. Olin Mathieson Chem. Corp.*, 253 F.2d 156, 161-64 (4th Cir. 1958).

No marked change in functionality occurs within the context of isolated genes. Booth, Katherine, *Isolated DNA Patents: Incentivizing Medical Research or Selling Human Identity: Association for Molecular Pathology v. U.S. Patent and Trademark Office*, 40

J.L. MED. & ETHICS 413, 414-15 (2012). Isolated genes are not materially different from their native counterparts. *Id.* Genetic coding sequence that is the subject of each of the BRCA gene claims remains the same whether the gene is in the human body or isolated (although chemical bonds may be altered through the process). 5 Alberts et al., *The Molecular Biology of The Cell* 552 (2008) (DNA sequencing involves the cutting of chromosomal DNA into fragments and the inserting of said DNA fragments into a self-replicating genetic element.). The only difference between the naturally occurring genes, like BRCA, and an isolated DNA sequence is that the isolated sequence has essentially been "cut" as a fragment from the original, naturally occurring sequence. *See id.* Indeed, isolated genes may be better analogized to "new mineral discovered in the earth," or the "new plant found in the wild." *See Chakrabarty*, 447 U.S at 309.

Ultimately, Myriad has failed to demonstrate at all that the isolated genes' origins lie in Myriad's inventive act. Their respective patents in human genes are not sustainable as an invention in a constitutional sense, as embodied in the relevant statutory and common law forms.[5]

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[5] Myriad may be able to claim (like the compilations at stake in *Feist*) that its related methods are the subject of an inventive act. *See Feist*, 499 U.S. at 348. The method claims, however, may be subject to other constitutional infirmities, as discussed *infra* in Part II.

II. GRANTING PATENTS ON HUMAN GENES AND RELATED METHODS PLACES A RANGE OF CONSTITUTIONAL VALUES AT RISK.

A. Assessing Whether Human Genes are Patentable Requires an Analysis of All Relevant Constitutional Provisions.

An improvidently granted patent may cause direct constitutional harm to those interested in a properly functioning patent system. Social interests in a functioning patent system are many and varied: scientists, researchers, and engineers creating advances in technology; manufacturers and designers implementing and vending these advances in the marketplace; and consumers putting these inventions and discoveries to their own uses. Although these stakeholders benefit from patent policy functioning properly, they are also uniquely positioned to suffer direct constitutional harms that stem from the issuance of such patents.

As discussed *supra*, the specific doctrinal content of patent law may have speech protective elements, such as the constitutional perquisite of invention, as embodied in its statutory and common law forms. The existence of such "built-in" accommodations may not be sufficient in *all* cases. An improvidently granted patent may like a poorly drafted statute, create such significant constitutional harm to such a wide range of plaintiffs, that further remedies beyond the scope of the internal doctrinal content of patent law merit consideration.

Here, stakeholder plaintiffs are at risk of suffering a variety of direct constitutional harms, caused by the issuance of patents on genetic material, that include direct harm to speech interests under the First Amendment, and dignity interests under the Thirteenth Amendment. Although the issuance of a copyright or patent will, necessarily, impact speech rights in some capacity, the issuance of a patent over genetic material itself is a substantial and impermissible intrusion into the speech rights of numerous potential third party plaintiffs, including researchers, patients, physicians and research groups. Likewise, the issuance of an improvidently granted patent may intrude upon the dignity interests associated with the Thirteenth Amendment.[6]

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[6] This is why the Declaratory Judgment Act exists as an alternative procedural vehicle in patent law insofar as it requires an into "*all the circumstances* . . . there is a substantial controversy, between parties having adverse legal interests." *MedImmune v. Genentech, Inc.*, 549 U.S. 118, 127 (2007) (quoting *Maryland Cas. Co. v. Pacific Coal & Oil Co.*, 312 U.S. 270, 273 (1941)). The Declaratory Judgment Act therefore exists as an integral alternative vehicle within the context of patent infringement because it permits diverse kinds of injury-in-fact to be alleged by diverse categories of declaratory judgment plaintiffs. The remedial structure of the Declaratory Judgment implies an inquiry into the standing of a respective plaintiff is not necessarily dependent on equivalent standing under the Patent Act. Interested third-party plaintiffs, therefore, must be allowed to bring constitutional claims of harm.

B. Human Gene Patents and Their Related Methods Place First Amendment Values at Risk by Improperly Impeding the Exchange of Ideas and Access to Important Information.

Myriad's improvidently granted patents in human genetic material and associated diagnostic methods inhibit the communicative discourse that would otherwise occur in academic fields devoted to genomic science and in clinical health care settings. In particular, human gene patents create "monopolies of expression" that prevent searching inquiry in the context of the scientist's laboratory and sharing information fully in the context of the physician's office. Public health communications and counseling efforts are similarly curtailed. *See* David Lange & H. Jefferson Powell, *No Law: Intellectual Property in the Image of An Absolute First Amendment* 305 (2009).

Specific constitutional harm can be significant and direct under the relevant factual circumstances. Research organizations have claimed that Myriad's enforcement of its patents in basic genetic information prevents their members from undertaking further scientific inquiry. Individual researchers, clinicians and health care providers maintain that Myriad's enforcement of its patents has chilled research and compromised communications with patients. As a result other patients are denied access to information important for making crucial medical decisions with respect to an appropriate course of care in consultation with their health care providers.

1. Human Gene Patents Harm Communicative Discourse in Scientific Communities.

First Amendment values instruct that a vibrant marketplace of ideas requires open access to the storehouse of knowledge. As this Court explained in *Red Lion Broadcasting Co. v. FCC*, "[I]t is the purpose of the First Amendment to preserve an uninhibited marketplace of ideas in which truth will ultimately prevail, rather than to countenance monopolization of that market, whether it be by the Government itself or a private licensee." *Red Lion Broadcasting Co. v. FCC*, 395 U.S. 367, 390 (1967). An improvidently granted patent may remove essential information from the marketplace of ideas and "contract the spectrum of available knowledge" inconsistent with "the spirit of the First Amendment." *Griswold v. Connecticut*, 381 U.S. 479, 482 (1965).

Scientific inquiry necessarily involves shared discourse between researchers within a discipline; patents granted in these "vocabulary" or "building blocks" of discourse may impede such freedom. *See* Barry P. McDonald, *Government Regulation or Other "Abridgments" of Scientific Research: The Proper Scope of Judicial Review Under the First Amendment*, 54 EMORY L. REV. 979, 997 (2005) (advocating a strict standard of review for actions which "significantly curtail a given area of research by impeding the data gathering efforts and thus curtail scientific expression related to that research"); *see also Laboratory Corp. of America v. Metabolite Labs., Inc.*, 548 U.S.

124, 125 (2006) (An improperly issued patent can force researcher's to engage in "costly and time-consuming searches of existing or pending patents, by requiring complex licensing arrangements, and by raising the costs of using that patented information, sometimes prohibitively so.")

Human gene patents restrain academic inquiries and scientific processes crucial to innovation and natural world comprehension. "In science, the relation between experiment and free thought is familial. Although the pursuit of knowledge is not the summum bonum but only one good among many, one hesitates to impede it or to set a precedent that might be used to inhibit other socially controversial precedent." Stephen Breyer & Richard Zeckhauser, *The Regulation of Genetic Engineering*, 1 Man & Medicine 1, 12 (1975).

Human gene patents inhibit scientific innovation in this area because this genetic material constitutes a "staple" public good that needs to be accessible to a range of users as a basic precondition for inquiry and innovation. *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 131 (1948) (This Court prohibits the issuance of patents when the issuance "restrict[s] free access to materials already available."); *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 5-6 (1966). This Court also cautions against enlarging a patent monopoly "without regard to the innovation, advancement or social benefit gained thereby." *Id.* This reflects a judgment that patent protection in certain cases impedes, rather than promotes, scientific progress. *See Metabolite Labs., Inc.*, 548 U.S. 124, 127-28 (Breyer, J., dissenting).

2. Patents on Diagnostic Methods Impede Access to Information in Health Care Contexts.

Claims on diagnostic methods associated with human genetic material impede access to information, thus harming patients' and the general publics' "right to receive information and ideas" that pertain to health risks. *See, e.g., Stanley v. Georgia*, 394 U.S. 557, 564 (1969); *see also Kleindienst v. Mandel*, 408 U.S. 753, 762-63 (1972) (citing cases).

The right to receive information is an inherent corollary of the right of free speech explicitly guaranteed by the Constitution. *See, e.g., Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748, 756-57 (1976). The right to receive ideas follows ineluctably from the sender's First Amendment right to send them for "dissemination of ideas can accomplish nothing if otherwise willing addressees are not free to receive and consider them." *Lamont v. Postmaster General*, 381 U.S. 301, 308 (1965) (Brennan, J., concurring). As the right to receive ideas is a necessary predicate to the recipient's meaningful exercise of his own rights of speech, press, and political freedom, the ability to receive information about genes is predicate to being at liberty to make meaningfully informed decisions in matters concerning health and bodily integrity.

Physicians and patients enjoy a protected freedom of expression in the context of the physician-patient relationship that is compromised by patents on the diagnostic methods claimed by Myriad. An early formulation of the right to receive information was advanced in the context of the physician-patient relationship. In *Griswold v. Connecticut*, the Supreme Court held the "right of freedom of speech and press includes not only the right to utter or to print, but [also] . . . the right to receive . . . " *Id.* The Supreme Court has rejected restraints on freedom of expression that would place physicians in an "undesired and uncomfortable straightjacket." *Planned Parenthood of Missouri v. Danforth*, 428 U.S. 52, 67 (1976). Because it remains the responsibility of the physician to ensure that appropriate information is conveyed to their patients based on the condition of the patient, *City of Akron v. Akron Ctr. for Reproductive Health*, 462 U.S. 416, 443 (1983), the Supreme Court has consistently cleared "obstacles in the path of the doctor" upon whom patients are entitled to rely for advice in connection with health care decisions. *Id.* (citing *Whalen v. Roe*, 429 U.S. 589, 604 n.33 (1977)). In the physician-patient relationship, patients expect that physicians will not withhold relevant information regarding care options and consequences. *Rust v. Sullivan*, 500 U.S. 173, 211 n.3 (Blackmun, J., dissenting) ("[I]n our society, the doctor-patient dialogue embodies a unique relationship of trust . . . each of us attaches profound importance and authority to the words of advice spoken by the physician."); *id.* at 218; *Conant v. Walters*, 309 F.3d 629, 644 (9th

Cir. 2002) (Kozinski, J., concurring) (explaining that "the harm to patients from being denied the right to receive candid medical advice is far greater than the harm to doctors from being unable to deliver such advice" and noting that "for patients who suffer from horrible disabilities. . . . [e]nforcement of the federal policy [would] cut such patients off from competent medical advice and leave them to decide on their own"). Physicians seeking to provide complete information to a patient concerning a predisposition for developing breast or ovarian cancer allege they have been constrained by the patents at issue.

The diagnostic methods in question also provide significant restraints on public health advocates in the dissemination of genetic information to targeted communities. The ability of communities to receive information about health-related risks is crucial for a functional public health system. *See* Wendy Parmet, *Public Health and Constitutional Law: Recognizing the Relationship*, 10 J. HEALTH CARE L. & POL'Y 13, 22 (2007). Speech is crucial to the dissemination of relevant health care information. Wendy Parmet & Jason Smith, *Free Speech and Public Health: A Population-Based Approach to the First Amendment*, 39 LOY. L.A. L. REV. 363, 376 (2006) ("[S]peech helps to mold the informational environment, which itself serves as one of the many factors that influence a population's health."). The specific diagnostic patents here may cause significant harm within a newly developing field of public health, by limiting speech within the context of genetic counseling. Genetic counselors within these organizations would serve as the messengers of crucial health information, were their First Amendment rights not curtailed by the existence of an invalid patent in the diagnostic methods associated with this patent. *See generally* Alexandra Minna Stern, *Telling Genes: The Story of Genetic Counseling in America* (2012) (assessing the role of genetic counseling in public health communications). While genetic counselors would like to offer systematic gene diagnosis, the diagnostic methods patents at issue here may offer a significant barrier to such efforts.

C. Human Gene Patents Implicate the Respect for Human Dignity Inherent in the Non-Commodification Principle Embodied in the Thirteenth Amendment.

The Thirteenth Amendment provides that "[n]either slavery nor involuntary servitude . . . shall exist in the United States." U.S. Const. amend. XIII. Among its other meanings, the Thirteenth Amendment can be seen to prohibit ownership of and control over another human being for pecuniary gain. George Rutherglen, *State Action, Private Action, and the Thirteenth Amendment*, 94 VA. L. REV. 1367, 1382 (2008) (observing that Congressional passage of the Thirteenth Amendment "concerned rights directly opposed to one another: what the slaveowners lost in property rights, the slaves gained in freedom"); *see also Plessy v. Ferguson*, 163 U.S. 537, 542 (1896) (defining slavery as "the absence of a legal right to the disposal of his own person, property, and services"). The Thirteenth Amendment prohibition of a property claim in a person suggests a constitutional recognition that eliminating a category of property interest in humans may act to preserve the human dignity inherent in a claim of personhood. *See generally* Leslie Meltzer Henry, *The Jurisprudence of Dignity*, 160 U. PA. L. REV. 169, 202 (2011) (discussing dignity). This principle could aptly be termed a non-commodification principle. *See Moore v. California Regents*, 793 P.2d 479, 515-17 (Cal. 1990) (Arabian, J., concurring) (expressing concern that commercialization of human cells could endanger the basic concept of human dignity violating the Thirteenth Amendment).

The non-commodification principle contained within the Thirteenth Amendment has been recognized within the domestic and international patent regime itself. In 2011, Congress prohibited a patent from issuing "on a claim directed to or encompassing a human organism." *See* 35 U.S.C. § 101 (2012); Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011). The United States Patent and Trademark Office in 1987 recognized that "[a] claim directed to or including within its scope will not be considered to be 'patentable subject matter' [because] the grant of a property right in a human being is prohibited by the Constitution." U.S. Patent and Trademark Office, PTO Policy on Patenting of Animals (April 7, 1987), *reprinted in* U.S. Congress, Office on Technology Assessment, New Developments in Biotechnology: Patenting Life 93 (1990). The non-commodification principle has also been recognized in the international patent regime. For example, the European Council Convention of Human Rights and Biomedicine, provides that "the human body and its parts shall not . . . give rise to financial gain." Convention on Human Rights and Biomedicine art. 21, *opened for signature* Apr. 4, 1997, E.T.S. No. 164, *available at* http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm; *see also* Deryck Beyleveld & Roger Brownsword, *Human Dignity, Human Rights, and Human Genetics*, 61 MOD. L. REV. 661, 671 (1998) (Commercializing human genes must be conducted on the "basis of free choice" in order to protect parties in those circumstances when there are "significant asymmetries of information and bargaining strength between the parties.")

Patents in human genes do not claim the whole person; however, genetic material is a constituent element of any person and is essential to and embodied within every human life form. Our current patent regime provides insufficient ethical guidance to ensure that patents are properly granted in genetic material. For example, while the European Patent Office has recognized that the potential isolation of genetic material may be patentable, it has done so only after ensuring that those who have donated the basic material have done so in a consensual, non-coercive manner. *See* In re Relaxin, EPO 6/1995, 398-99 ("With regard to the isolation of mRNA from tissue taken from pregnant women, the proprietor stated that the women who donated tissue consented to do so within the framework of necessary gynecological operations.") Our patent examination process lacks these essential procedural safeguards. This further suggests that human patent genes create substantial constitutional harm under the Fourteenth Amendment as well as the Thirteenth Amendment, and thus should be subject to searching judicial intervention into whether such claims should be made permissible through an individualized patent examination process that lacks sufficient constitutional safeguards for the rights of third-parties that may be impacted by an improvidently granted patent. See Beyleveld & Brownsword, 61 MOD. L. REV. at 676 ("[W]e might seek ways of strengthening [consent] procedures or we might advocate a general prohibition on gene commerce (as the lesser of two evils, and for the sake of protecting the interests of vulnerable agents").

◆

CONCLUSION

Patents on human genes serve to limit paths of inquiry rather than spur innovation. Human gene patents operate as roadblocks, forcing detours and delaying new discoveries. This result runs counter to the incentive structure that informs the patent system that rewards those who "invent and discover." Myriad's patents on human genes fail the constitutional requirement of invention, embodied in its statutory form because they do not derive from a basic level of creativity.

The existence of human gene patents and related diagnostic methods run counter to the core values protected in the First Amendment. The First Amendment exists to protect the marketplace of ideas and promote access to the storehouse of knowledge. Patents on diagnostic methods associated with human genetic material serve to restrict access to knowledge, to reduce the communicative conduct of scientific inquiry and to retard services that could improve the public's information concerning health risks.

These patents in effect place a price on the building blocks of humanity and personhood. This implicates the non-commodification principle embodied in the Thirteenth Amendment and threatens the liberty and dignity of persons protected by the Constitution.

For these reasons, we respectfully ask this Court to invalidate Myriad's patents.

Respectfully submitted,

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AMICUS
CURIAE
BRIEF

RECORD
AND
BRIEFS

Supreme Court, U.S.
FILED
MAR 14 2013
OFFICE OF THE CLERK

No. 12-398

IN THE
Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,
Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF FOR THE NANOBUSINESS COMMERCIALIZATION ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENTS

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RULES

Supreme Court Rule 37 1

INTEREST OF *AMICUS CURIAE*

The NanoBusiness Commercialization Association ("NanoBCA") submits this brief as amicus curiae in order to ensure that the United States continues to lead the world in the burgeoning field of nanotechnology—a leadership position achieved in large part due to the country's robust patent system that encourages private investment in high-risk, cutting-edge research and commercialization.[1]

About NanoBCA. NanoBCA is a 501(c)(6) trade organization dedicated to promoting the commercialization of nanotechnology and helping companies bring affordable, life-improving nanotech products to market. NanoBCA's vision is to ensure that the United States—its companies, universities and people—leads the world in the discovery and commercialization of nanotechnology, and that nanotechnology's benefits are delivered safely to all of society. Among its missions, NanoBCA advocates for continued U.S. investment in nanotechnology through the National Nanotechnology Initiative ("NNI")—the U.S. government's interagency program launched in 2001 for coordinating research and development and enhancing collaboration in nanoscale science, engineering and technology. Congress codified and expanded the NNI by passing the 21st Century Nanotechnology Research and Development Act of 2003, Pub. L. No. 108-153, 117 Stat. 1923 (2003).

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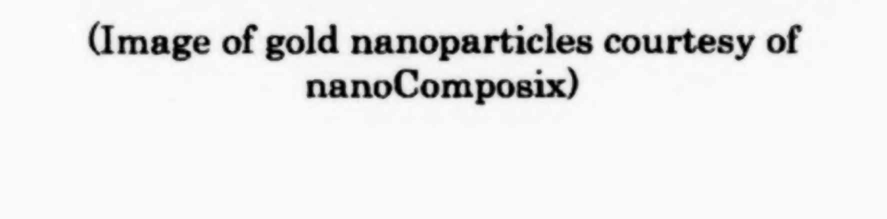
[1] In accordance with Supreme Court Rule 37.6, amicus curiae states that this brief was not authored, in whole or in part, by counsel to a party, and that no monetary contribution to the preparation or submission of this brief was made by any person or entity other than the amicus curiae or its counsel. Petitioners have filed a letter of blanket consent to *amici* on January 2, 2013. Respondents granted consent to *amicus* on February 15, 2013, via electronic mail, a copy of which is being submitted herewith.

What is nanotechnology? "Nanotechnology is the understanding and control of matter at the nanoscale, at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications." NATIONAL SCIENCE & TECHNOLOGY COUNCIL, NATIONAL NANOTECHNOLOGY STRATEGIC PLAN 3 (2011). A nanometer is one-billionth of a meter. A human hair is approximately 80,000 to 100,000 nanometers wide. A DNA molecule is approximately 2.5 nanometers wide; its uncoiled length can range from several to millions of nanometers.

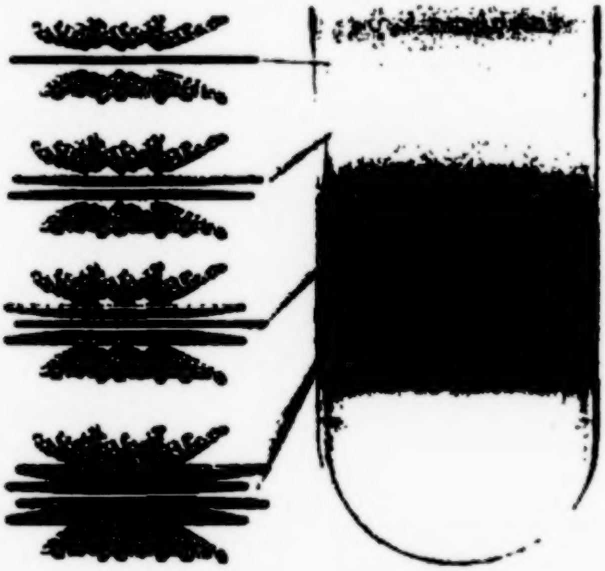
What is unique about nanomaterials that have been "isolated" from bulk materials? At the nanoscale, quantum physics begin to dominate the behavior and properties of materials. This quantum effect causes unusual physical, chemical, and biological properties to emerge when materials are reduced in size to the nanoscale. The properties of these man-made "nanomaterials" often differ in dramatic and unexpected ways from the properties of bulk materials found in nature, from which nanomaterials can be said to have been "isolated" (e.g., mechanically cleaved to remove surrounding bulk material, or synthesized to contain a tiny fraction of the atoms or molecules found in bulk materials). There are numerous examples of man-made nanomaterials, "isolated," as it were, from their bulk constituents, which have enabled groundbreaking, real-world applications. Below are just a few examples.

- *Gold nanoparticles* can be thought of as "isolated" clusters of gold. At large scales, gold is shiny and yellow. But at the nanoscale, gold can vary in color from pink to red to purple depending on the size of the nanoparticles (seen below ranging from 5 to 100 nanometers in diameter). The unique properties of gold nanoparticles have enabled new diagnostic sensors and cancer therapies. For example, because gold nanoparticles selectively accumulate in tumors, they have enabled precise imaging and targeted laser destruction of tumors without harming surrounding healthy cells. *See* Nano.gov, What's So Special about the Nanoscale?, http://nano.gov/nanotech-101/special (last visited Mar. 4, 2013).



(Image of gold nanoparticles courtesy of nanoComposix)

- *Graphene* is, conceptually, an "isolated" form of graphite (graphite being a black, naturally-occurring form of carbon). Graphene consists of a single-atom-thick sheet of carbon that scientists have peeled from graphite's surface via mechanical cleaving or chemical exfoliation. Unlike large-scale graphite, however, nanoscale graphene is a near-perfect electrical conductor and, therefore, has attracted enormous attention for use in future-generation electronic devices. *See* Yanqing Wu *et al.*, *High-Frequency, Scaled Graphene Transistors on Diamond-like Carbon*, 472 NATURE 74 (2011). Scientists are now able to selectively isolate one-, two-, and three- atomic layers of graphene (seen below as blue, red, and green bands, respectively, in contrast to black graphite).



See Alexander A. Green & Mark C. Hersam, *Solution Phase Production of Graphene with*

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SUMMARY OF ARGUMENT

The Court in this case should do two things. First, it should uphold the patent eligibility of Myriad's product claims under § 101. Second, and just as importantly, the Court should recognize patent law's longstanding "experimental use" exemption from infringement which allows the public to use a patented invention for the "purpose of philosophical [or 'scientific'] experiment, or to ascertain the verity and exactness of the [patent] specification," or for "ascertaining the sufficiency of the [invention] to produce its described effects," or "to experiment with and improve upon the patented subject matter." *In re Rosuvastatin Calcium Patent Litig.*, 703 F.3d 511, 527 (Fed. Cir. 2012); *Sawin v. Guild*, 21 F. Cas. 554, 555 (C.C.D. Mass. 1813) (No. 12,391) (Story, J.); *Whittemore v. Cutter*, 29 F. Cas. 1120, 1121 (C.C.D. Mass. 1813) (No. 17,600) (Story, J.).

In so holding, the Court would strike the right balance between encouraging investment in early stage technology and ensuring that patents do not block follow-on research aimed at studying, improving upon, or designing around the patented inventions. NanoBCA submits that it is better to allow broad patent eligibility and to simultaneously clarify the scope of the experimental use doctrine, as opposed to denying patent eligibility outright, which could chill investment in early stage technology, including nanotechnology.

ARGUMENT

I. COMPOUNDS ISOLATED BY MAN, WHICH DO NOT EXIST IN NATURE IN ISOLATED FORM, YIELDING NEW COMMERCIAL USES, ARE PATENT ELIGIBLE UNDER § 101

When Congress enacted 35 U.S.C. § 101 as part of the Patent Act of 1952, Congress explained that patentable subject matter in that section "include[s] anything under the sun that is ***made by man***." S. REP. NO. 82-1979, at 5 (1952) (emphasis added); H.R. REP. NO. 82-1923 (1952) (emphasis added). A product of nature is clearly not patent eligible under § 101 because it is not "made by man" but is made by Nature itself.

Following Congress' directive, this Court has reiterated that the dividing line between an unpatentable "product of nature" and a patent eligible "invention" under § 101 is ***human ingenuity***:

> As this Court held in *Chakrabarty*, "the relevant distinction" for purposes of § 101 is not "between living and inanimate things, but between products of nature, whether living or not, and ***human-made inventions***."

J.E.M. Ag Supply v. Pioneer Hi-Bred Int'l, 534 U.S. 124, 134 (2001) (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 313 (1980) (emphasis added).

This Court's clear distinction between patent-eligible "products of human invention" and patent-ineligible "products of nature," *J.E.M.*, 534 U.S. at 134, rests on a well-established framework that has long encouraged chemists, biologists, and materials scientists to isolate and purify active natural ingredients, which do not exist naturally in isolated and purified form, and when so modified, unlock new commercial uses unavailable in nature.

A. "Isolated" and "Purified" Forms of Natural Products Have Long Been Patent Eligible

In 1877, Louis Pasteur was issued U.S. Patent No. 141,072, titled "Improvement in the Manufacture of Beer and Yeast." The patent specification explains that Pasteur discovered that "pernicious germs," naturally present in brewer's yeast, was what caused beer and other products made from yeast to spoil or "vary in condition." U.S. Pat. No. 141,072, p. 1 (issued Jul. 22, 1873). By eliminating these germs, "beer may be produced which shall not vary in condition at any temperature." *Id.* at 1. The specification stressed that "[t]he employment of *pure yeast . . . is of prime necessity*—that is to say, yeast deprived of the germs by which the beer is liable to be affected." *Id.* p. 2 (emphasis added). Thus, in addition to claiming the method he used to obtain pure yeast, Pasteur's patent also claimed: "*Yeast, free from organic germs of disease, as an article of manufacture.*" *Id.* p. 3, cl.2 (emphasis added).

In 1892, the Second Circuit in *Blumenthal v. Burrell* upheld the validity of a patent on a purified form of chymosin, an enzyme found in the stomach of pigs and used to curdle milk in the manufacture of cheese. 53 F. 105 (2d Cir. 1892). In nature, chymosin is always present with another enzyme, pepsin. The patent-in-suit claimed "chymosin separated from pepsin, and uncombined with foreign substances." *Id.* at 107. When "separated" as claimed, these enzymes "are perfectly soluble in water, and form tasteless and odorless and clear or limpid solutions that do not readily decompose." *Id.* at 106. Thus, despite the fact that chymosin "had long been used to curdle milk in the manufacture of cheese," the Second Circuit upheld the claim for purified chymosin, which the court held "was not merely an improved, but an absolutely new, article, having its own distinctive nature." *Id.* at 107.

In 1910, the Second Circuit in *Union Carbide Co. v. American Carbide Co.* upheld a claim to calcium carbide in crystalline form, which had existed previously only in amorphous (noncrystalline) form. 181 F. 104 (2d Cir. 1910). In both forms, however, calcium carbide has the identical chemical formula: CaC_2. *Id.* at 105. And in both forms, calcium carbide is useful in the production of acetylene gas. *Id.* But, unlike in amorphous form, crystalline calcium carbide "is more durable . . . hard, compact, and so unlike the [amorphous] powdery mass as almost to amount to a new body." *Id.* at 107. The court reasoned, "To hold an important discovery which has given to the world a commercially new product—a product the high utility of which must be conceded—not entitled to protection for want of novelty, would, as it seems to us, be applying the patent statute to defeat its fundamental purposes." *Id.* at 108.

That same year in *Kuehmsted v. Farbenfabriken of Elberfeld Co.*, the Seventh Circuit sustained a patent directed to "Aspirin"—acetylsalicylic acid in "substantially pure" form. 179 F. 701, 704 (7th Cir. 1910). The court accepted the defendant's assertion that acetylsalicylic acid, having "the same chemical formula" as the claimed compound, had previously been produced in impure form. *Id.* Those impurities, however, render the acid "undesirable or unsafe, if effective at all, in therapeutics." *Id.* In upholding the claim to the purified version, the court stated, "*it makes no difference, so far as patentability is concerned, that the medicine thus produced is lifted out of a mass that contained, chemically, the compound*; for, though the difference between [the patent] and [the prior art] be one of purification only—strictly marking the line, however, where the one is therapeutically available and the others were therapeutically unavailable—patentability would follow." *Id.* at 105 (emphasis added).

In 1911, Judge Billings Learned Hand, then a trial judge, authored *Parke-Davis & Co. v. H. K. Mulford Co.*, upholding a patent to a purified extract of animal adrenal glands "practically free from inert and associated gland-tissue." 189 F. 95, 98 (S.D.N.Y. 1911), *aff'd in part, rev'd in part*, 196 F. 496 (2d Cir. 1912). Before the Patent Office, counsel for applicant persuaded the examiner that "the substance as claimed is distinguished from the glands by the [claim] language that it is in stable and concentrated form and free from inert constituents." *Park-Davis*, 196 F. 496 (Transcript of

Record, No. 4363, Box 1684, at 851-853). At trial, defendants sought to invalidate the patent on the ground that "the patent [was] only for a degree of purity, and therefore not for a new 'composition of matter.'" *Parke-Davis*, 189 F. at 103. Judge Hand responded that "no one had ever isolated a substance which was not in salt form, and which was anything like" the patented product. *Id.* Judge Hand went on to famously say:

> But, *even if it were merely an extracted product without change, there is no rule that such products are not patentable.* Takamine was the first to make it available for any use by removing it from the other gland-tissue in which it was found, and, while *it is of course possible logically to call this a purification of the principle*, it became for every practical purpose a new thing commercially and therapeutically. That was a good ground for a patent.

Id. (emphases added).

In 1958, the Fourth Circuit in *Merck & Co. v. Olin Mathieson Chemical Corp.* reversed a district court's invalidation of several product claims on "product of nature" grounds. 253 F.2d 157 (4th Cir. 1958). The claims covered a purified form of vitamin B-12 obtained from fungi fermentation. Vitamin B-12 is produced naturally in minute quantities in the liver of cattle and in certain microorganisms. *Id.* at 161. These natural forms of vitamin B-12, the court found, have "no utility, therapeutically or commercially, until converted into compositions comparable to the patented products." *Id.* Moreover, "[vitamin B-12] did not exist in nature in the form in which the patentees produced it." *Id.* at 164. Citing *Union Carbide, Kuehmsted,* and *Parke-Davis,* the Fourth Circuit held:

> The compositions of the patent here have all of the novelty and utility required by the [Patent] Act [of 1952] for patentability. They never existed before; there was nothing comparable to them. *If we regard them as a purification of the active principle in natural fermentates, the natural fermentates are quite useless,* while the patented compositions are of great medicinal and commercial value. The step from complete uselessness to great and perfected utility is a long one.

Id. (emphasis added).

These cases established the well-settled rule that natural compounds, isolated and purified by man, which do "not exist in nature in the form" claimed (*Merck*)—and despite having "the same chemical formula" (*Kuehmsted*) or having been "extracted . . . without change" (*Parke-Davis*)—are patent-eligible human-made inventions, so long as they yield a new and improved utility over Nature. As such, the isolated/purified compounds are deemed "a commercially new product" (*Union Carbide*) "a new thing commercially and therapeutically" (*Parke-Davis*).[2]

B. The Word "New" in § 101 is Defined in § 102 and Nowhere Else

Section 101 requires patentable inventions to be "new and useful." But the word "new" in § 101 does not allow courts to expand its meaning beyond the novelty requirement of § 102. As Congress explained when it enacted both of these sections, "Section 102 . . . includes, in effect, an amplification and *definition of 'new' in section 101*." S. REP. NO. 82-1979, at 6 (emphasis added); H.R. REP. NO. 82-1923, at 7 (emphasis added).

Prior to 1952, a single statutory provision governed both patent eligibility and patentability (R.S. § 4886, codified at 35 U.S.C. § 31). In the Patent Act of 1952, this old provision was "split into two sections, section 101 relating to the subject matter for which patents may be obtained, and section 102 defining statutory novelty and stating other conditions for patentability." S. REP. NO. 82-1979, at 17; H.R. REP. NO. 82-1923, at 17.

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[2] *See* EDWARD THOMAS, CHEMICAL PATENTS AND ALLIED PATENT PROBLEMS, 32 (John Byrne & Co. 1917) ("A product may be patentable because of its utility even if merely purer or in more useful form than the prior art shows."); *id.* at 33 ("A product may be patentable because it has hitherto been unattainable . . . ."); *id.* at 34 ("It is the utility which is controlling, and a composition having new utility, not previously obtainable by those skilled in the art is patentable even though it differs from another only in degree.").

The fact that, prior to 1952, patent eligibility and novelty resided in the same statutory section explains some of today's confusion, seen in various briefs submitted to this Court, which tend to conflate these two distinct requirements when relying on earlier cases, but which cases were clearly decided on lack of novelty grounds, not on patent-eligibility grounds. *See, e.g., Am. Wood-Paper Co. v. Fibre Disintegrating Co.*, 90 U.S. 566, 596 (1874) (holding that patent on cellulose derived from wood was "void for want of novelty"; "no substantial difference is discoverable"; "the product was in no sense new"); *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 308, 311 (1884) (citing *American Wood-Paper* to hold that artificial alizarine—claimed "not as a new substance prepared for the first time, but as the substance already known as alizarine"—was an "old article," indeed a "well known substance").

C. Sufficiency of "Differences" Between a Man-Made Compound and Its Natural Precursor is Measured under § 103

Chakrabarty stated that the man-made bacteria at issue in that case exhibited "*markedly different* characteristics from any found in nature." 447 U.S. at 310 (emphasis added). But *Chakrabarty* did not hold that the existence of "markedly different characteristics" is always a necessary condition under § 101. Nor did the Court attempt to lay out any fact-intensive framework for deciding in future case whether differences between a claimed and natural product are sufficiently different to be regarded as "markedly" different. Indeed, technical fact-finding of this sort is not suitable to § 101, which has always been a pure question of law.

Fortunately, Congress has provided an exact (and only) standard for weighing any "differences" that may exist between what a patent claims to be new and what the world knows to be old. Section 103 asks "if the *differences* between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a) (emphasis added). Section 103 involves "several basic factual inquiries," treated as questions of fact, that underlie the ultimate legal question of obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966) (identifying such factors as "[1] the scope and content of the prior art . . . [2] differences between the prior art and the claims at issue . . . [3] the level of ordinary skill in the pertinent art . . . . [4] secondary considerations").

Section 103 is, therefore, the only appropriate test for weighing the sufficiency of any "differences" between a man-made product and the natural building blocks from which the product is derived. Since all patents must pass through § 103, it applies with equal force to claims on isolated DNA. *See In re Kubin*, 561 F.3d 1351, 1354 (Fed. Cir. 2009) (affirming as obvious a claim to an isolated DNA sequence, even where the exact sequence could not have been predicted, since the claimed sequence could readily have been obtained using convention techniques, with knowledge of mouse versions of human receptor proteins).

D. *Funk Brothers* Dealt with Pre-1952 Act "Invention" (Today's § 103 Obviousness), Not § 101 Patent Eligibility

Petitioners and the United States are wrong to characterize *Funk Brothers* as a "Section 101" case. Pet. Br. 28; U.S. Br. 14-15.

Section 101 did not exist in 1948 when *Funk Brothers* was decided. More importantly, *Funk Brothers* did not deal whatsoever with patent eligibility but instead addressed the requirement of "invention" or "discovery"—today's nonobviousness requirement. *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 132 (1948) (holding that "the product claims do not disclose an *invention or discovery* within the meaning of the patent statutes" (emphasis added)). In setting forth the rule that a patentable product must "satisfy the requirement of invention or discovery," *id.* at 131, *Funk Brothers* cites *Cuno Engineering*, a case involving mechanical cigar lighters—not anything resembling a product of nature. *Cuno Eng'g Corp. v. Automatic Devices Corp.*, 314 U.S. 84, 85-86 (1941) (the "claims in question are for improvements in lighters, commonly found in automobiles, for cigars, cigarettes and pipes"). And *Cuno Engineering* in turn traces the origin of the "invention" requirement to *Hotchkiss*: "Since *Hotchkiss v. Greenwood*, [52 U.S. 248] 11 How. 248, 267, decided in 1851, it has been recognized that if an improvement is to obtain the privileged position of a patent more ingenuity must be involved than the work of a mechanic skilled in the art." *Cuno Eng'g*, 314 U.S. at 90.

In 1952, Congress for the first time codified the common-law "invention" requirement as the new statutory nonobviousness requirement of § 103. The Committee Reports state that one of the "major changes" in the 1952 Patent Act was "incorporating a *requirement for invention* in § 103." S. REP. NO. 82-1979, at 4 (emphasis added); H.R. REP. NO. 82-1923, at 5 (emphasis added). This Court has explained that in enacting § 103, "Congress has emphasized 'nonobviousness' as the operative test of the section, rather than the less definite 'invention' language of *Hotchkiss* [*v. Greenwood*, 52 U.S. 248 (1851)] that Congress thought had led to 'a large variety' of expressions in decisions and writings." *Graham*, 383 U.S. at 14 (quoting S. REP. NO. 82-1979, at 6; H.R. REP. NO. 82-1923, at 7).

Properly viewed in this light, *Funk Brothers* is a classic case of a non-inventive, or § 103 obvious, combination of individually known elements (six known bacteria cultures), combined using conventional techniques (mixing and packaging), with no change in each element's respective function (each culture inoculating the same crop it inoculates separately). It is a textbook example of pre-1952 "lack of invention," or post-1952 obviousness. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

E. *American Fruit Growers* Interpreted "Manufacture," and Not "Composition of Matter"

The sole question in *American Fruit Growers, Inc. v. Brogdex Co.* was:

> Is an orange, the rind of which has become impregnated with borax, through immersion in a solution, and thereby rendered resistant to blue mold decay, a *"manufacture," or manufactured article*, within the meaning of § 31, Title 35, U.S. Code?

283 U.S. 1, 11 (1931) (emphasis added). The Court answered in the negative, relying on the dictionary definition of "manufacture," defined as "'the production of articles for use from raw or prepared materials by giving to these materials *new forms, qualities, properties, or combinations*, whether by hand-labor or by machinery.'" *Id.* (quoting CENTURY DICTIONARY). Because the addition of borax to the rind did not change "the name, appearance, or general character of the fruit," and remained "fit only for the same beneficial uses as theretofore," it did not qualify as a "manufacture." *Id.* at 11-12.

By contrast, *Chakrabarty* squarely addressed the "composition of matter" category of § 101. The Court observed that "'composition of matter' has been construed consistent with its common usage to include 'all compositions of two or more substances and . . . all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids.'" *Chakrabarty*, 447 U.S. at 308 (quoting *Shell Development Co. v. Watson*, 149 F.Supp. 279, 280 (D.C. Cir. 1957) (citing 1 A. DELLER, WALKER ON PATENTS § 14, p. 55 (1st ed. 1937))). In holding that "respondent's micro-organism plainly qualifies as patentable subject matter," and not an unpatentable product of nature, the Court explained that the "claim is not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity 'having a distinctive name, character [and] use.'" *Id.* at 309-310 (quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887)).

F. Myriad's Isolated DNA Claims Do Not Cover "Products of Nature"

Isolated DNA is not a "product of nature" since it is made "isolated" only through human ingenuity and manipulation. No natural thing can possibly infringe a patent on isolated DNA since no natural thing possesses DNA in isolated form. Also, isolated DNA is commercially useful in a way that native DNA is not: it allows individuals to be tested for diseases outside the human body. This utility is possible only when DNA is isolated; otherwise, DNA is entirely useless for such purpose in its native state, as Petitioners concede. Pet. Br. 9 ("It is not currently possible to use genes, including looking at or sequencing them, without removing or 'isolating' them from the body.").

Congress recently took up the issue of "gene patents" in the Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 27(a), 125 Stat. 338 (2011). Rather than categorically excluding them from patent protection (as it did with patents encompassing a "human organism"[3] or a method of "reducing, avoiding, or deferring tax liability"[4]), Congress instead directed the U.S. Patent and Trademark Office to "conduct a study on effective ways to provide independent, confirming genetic diagnostic test activity where gene patents and exclusive licensing for primary genetic diagnostic tests exist." *Id.* at § 27(a). Thus, Congress expressly recognized that "gene patents . . . exist," and instead of banning them like it did with other technologies, decided that more study was needed. Informed by this study (or not), Congress is free to amend § 101 so as to exclude from patent protection isolated DNA. *Cf. Chakrabarty*, 447 U.S. at 318 ("Congress is free to amend § 101 so as to exclude from patent protection organisms produced by genetic engineering."). "But, until Congress takes such action, this Court must construe the language of § 101 as it is." *Id.*

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[3] *Id.* at § 32(a) ("[N]o patent may issue on a claim directed to or encompassing a human organism.").

[4] *Id.* § 14(a) ("[A]ny strategy for reducing, avoiding, or deferring tax liability, whether known or unknown at the time of the invention or application for patent, shall be deemed insufficient to differentiate a claimed invention from the prior art.").

Whether ultimately Myriad's claims are *patentable*, however, is a different question entirely. NanoBCA takes no position on whether the claims satisfy the requirements of novelty (§ 102), nonobviousness (§ 103), written description and enablement (§ 112 (a)), definiteness (§ 112 (b)), or any of the other "conditions or requirements of this title" which may preclude patentability. 35 U.S.C. § 101.

II. PATENTS DO NOT PREEMPT OTHERS FROM EXPERIMENTING ON, IMPROVING UPON, OR DESIGNING AROUND A PATENTED INVENTION

Petitioners assert that Respondents' patents "preempt" others from studying BRCA genes, using them to develop better tests or treatments, or discovering new uses for them in the detection of other cancers. Pet. Br. 2-3, 25, 40-48. This Court should dismiss these arguments and expressly recognize patent law's longstanding infringement defense based on "experimental use," first articulated by Justice Joseph Story in 1813, and followed by various lower courts. *See Whittemore v. Cutter*, 29 F. Cas. 1120 (C.C.D. Mass. 1813) (No. 17,600).

This common law exception shields follow-on researchers from infringement liability in much the same way that a second, common law "experimental use" exception shields patentees from invalidity. The latter exception is likewise traced to Justice Story and is firmly established in this Court's precedents. *See Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 64 (1998) ("[A]n inventor who seeks to perfect his discovery may conduct extensive testing without losing his right to obtain a patent for his invention—even if such testing occurs in the public eye.").

A. This Court Recognizes an "Experimental Use" Exception for Patentees

In 1825, Justice Story, sitting as circuit justice in *Mellus v. Silsbee*, wrote that an inventor's patent should not be found invalid for lack of novelty if the inventor had licensed "a few persons" to use his invention in order to "ascertain its utility" prior to applying for the patent. 16 F. Cas. 1332, 1334 (C.C.D. Mass. 1825) (No. 9404). Justice Story revisited this theme twice more as circuit justice, explaining again that an inventor's own experiments, though conducted in public view, "would not take away his right to a patent" for lack of novelty, so long as the use of the invention was "merely experimental, to ascertain the value or utility, or success of the invention, by putting it in practice." *Wyeth v. Stone*, 30 F. Cas. 723, 726 (C.C.D. Mass. 1840) (No. 18,107); *Ryan v. Goodwin*, 21 F. Cas. 110, 111 (C.C.D. Mass. 1839) (No. 12,186).

This Court adopted the above view in *Elizabeth v. Pavement Co.*, holding that an inventor's public experimentation on an invention (in that case, an improved street pavement tested in plain sight) was not an invalidating "public use" within the meaning of the statute, "so long as the inventor is engaged, in good faith, in testing its operation." 97 U.S. 126, 135

(1878). "He may see cause to alter it and improve it, or not. His experiments will reveal the fact whether any and what alterations may be necessary." *Id.* "[A] bona fide effort to bring his invention to perfection, or to ascertain whether it will answer the purpose intended," is not an invalidating public use. *Id.* at 137. But "[a]ny attempt to use [the invention] for a profit, and not by way of experiment, . . . would deprive the inventor of his right to a patent." *Id.*

As recently as 1998, this Court in *Pfaff* stated, "The law has long recognized the distinction between inventions put to experimental use and products sold commercially." 525 U.S. at 64 (citing *Elizabeth*, 97 U.S. at 137). Looking back at the doctrine over nearly two centuries, the Court commented favorably that "[t]he experimental use doctrine, for example, has not generated concerns about indefiniteness." *Id.* at 67.

B. Since 1813, Lower Courts Have Recognized an "Experimental Use" Exception for Follow-On Researchers

Justice Story is also widely credited [5] with establishing an experimental use defense to patent infringement. Exactly two centuries ago, Justice Story sat as circuit justice in *Whittemore v. Cutter*, a case in which a patentee appealed a jury instruction that would have limited infringement to situations where an infringer had constructed an accused device that was "fit for use, and with a design to use it for profit." 29 F. Cas. 1120, 1121 (C.C.D. Mass. 1813) (No. 17,600). While acknowledging that this instruction was "certainly favorable to the defendant," Justice Story sustained this portion of the instruction on the basis that

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[5] *See, e.g.*, Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017, 1023 (1989).

> it could never have been the intention of the legislature to punish a man, who constructed such a machine merely for *philosophical experiments*, or for the purpose of *ascertaining the sufficiency of the machine to produce its described effects.*

Id. (emphases added). Notably, the word "philosophical" in Justice Story's day meant "scientific."[6]

That same year, in *Sawin v. Guild*, Justice Story, sitting again as circuit justice, revisited the experimental use defense and set forth the rule that infringement requires

> the making [of the invention] with an intent to use [it] for profit, and not for the mere purpose of *philosophical experiment*,

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[6] *See* Janice M. Mueller, *The Evanescent Experimental Use Exemption from United States Patent Infringement Liability: Implications for University and Nonprofit Research and Development*, 56 BAYLOR L. REV. 917, 929 (2004) ("Multiple authorities confirm that in Story's day philosophical meant scientific. At that time the noun philosophy referred to natural philosophy, which in turn meant science generally.").

> *or to ascertain the verity and exactness of the [patent] specification.*

21 F. Cas. 554, 555 (C.C.D. Mass. 1813) (No. 12,391) (emphasis added).

In 1818, this Court in *Evans v. Eaton*, a patent case, appended to its decision a comprehensive summary of the state of patent law, which included Justice Story's language (who was a member of the Court at the time) that "the making of a patented machine *fit for use, and with a design to use it for profit*, in violation of the patent right, is, of itself, a breach of this section, for which an action lies." 16 U.S. 454, app. 26 (1818) (citing *Whittemore*, 29 F. Cas. at 1121) (emphasis added).

In subsequent years, Justice Story's experimental use defense to patent infringement gained general acceptance in case law and treatises.[7] Defendants have successfully raised it to escape infringement in a number of cases over the years.[8] The Federal Circuit, in two cases where the defense was raised, found it not to apply to the particular facts in those cases.[9] Scholars nevertheless agree that these two holdings by the Federal Circuit are correct, even if dicta in those cases suggests a narrower defense than originally contemplated by Justice Story, given that in both cases the defendants used the patented inventions—not to study, or improve upon, or design around the patented inventions, as Justice Story would have permitted—but as a thing the defendants knew to be fit for its intended purpose, and used as such.[10]

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[7] *See, e.g.*, *Poppenhusen v. Falke*, 19 F. Cas. 1048, 1049 (C.C.S.D.N.Y. 1861) (No. 11,279) (calling the doctrine "well-settled"); 3 WILLIAM C. ROBINSON, THE LAW OF PATENTS FOR USEFUL INVENTIONS § 898, at 55-57 (Boston, Little, Brown & Co. 1890) (restating the doctrine).

[8] *See, e.g.*, *Chesterfield v. United States*, 141 Ct. Cl. 838, 845-46 (1958); *Ordnance Engineering Corp. v. United States*, 84 Ct. Cl. 1, 4 (1936); *Ruth v. Stearns-Roger Mfg. Co.*, 13 F. Supp. 697, 703 (D. Colo. 1935), *rev'd on other grounds*, 87 F.2d 35 (10th Cir. 1936); *Beidler v. Photostat Corp.*, 10 F. Supp. 628, 630 (W.D.N.Y. 1935); *Poppenhusen v. N.Y. Gutta Percha Comb Co.*, 19 F. Cas. 1059, 1063 (C.C.S.D.N.Y. 1858) (No. 11,283).

Last year, the Federal Circuit in *In re Rosuvastatin Calcium Patent Litigation*, returned to Justice Story's original, broad exception laid out in *Whittemore* (quoting in full his experimental use language) to reaffirm the broad view that "patenting does not deprive the public of the right to *experiment with and improve upon* the patented subject matter." *In re Rosuvastatin Calcium Patent Litig.*, 703 F.3d 511, 527 (Fed. Cir. 2012 (emphasis added).[11]

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[9] *Madey v. Duke University*, 307 F.3d 1351, 1362-63 (Fed. Cir. 2002); *Roche Products. Inc. v. Bolar Pharm. Co.*, 733 F.2d 858, 863 (Fed. Cir. 1984).

[10] *See* Harold C. Wegner, *Post*-Merck *Experimental Use and the "Safe Harbor,"* 15 FED. CIR. B.J. 1, 13, 15 (2005); Mueller, 56 BAYLOR L. REV. at 933-34, 940-41.

[11] *See also Momenta Pharms., Inc. v. Amphastar Pharms., Inc.*, 686 F.3d 1348, 1375 (Fed. Cir. 2012) (Rader, C.J., dissenting) (explaining that "patents properly remain a *tool for research and experimentation* because the system encourages publication and sharing of research results") (emphasis added).

C. This Court Should Likewise Recognize that Patents Do Not Preempt Follow-On Research

Just as a *patentee* may "conduct extensive testing without losing his right to obtain a patent for his invention," *Pfaff*, 525 U.S. at 64, so too may the *public* use a patented invention

- for the "purpose of philosophical [or 'scientific'] experiment,"
- "to ascertain the verity and exactness of the [patent] specification,"
- to "ascertain[] the sufficiency of the [invention] to produce its described effects," or
- "to experiment with and improve upon the patented subject matter."

Rosuvastatin, 703 F.3d at 527; *Sawin*, 21 F. Cas. at 555; *Whittemore*, 29 F. Cas. at 1121.

These two doctrines operate in parallel to negate or exclude "experimental use" from the word "use" in § 102(b) (novelty) and the word "uses" in § 271(a) (infringement), which have appeared together in essentially the same form since the nation's first patent act. *See* Patent Act of 1790, ch. 7, §§ 1, 4, 1 Stat. 109, 110, 111 (1970) (novelty: "not before known or *used*" (emphasis added); infringement: "[i]f any person or persons shall devise, make, construct, *use*, employ, or vend" (emphasis added)).

Besides sharing historical origins in Justice Story, the two experimental use doctrines promote similar policy goals: facilitating scientific research for the purpose of ensuring that patented inventions are properly understood, perfected, and improved upon—whether by the patentee or by the public. *See Elizabeth*, 97 U.S. at 135 (stating that a patentee may "test the [invention], and ascertain whether it will answer the purpose intended, and make such alterations and improvements as experience demonstrates to be necessary"); *Rosuvastatin*, 703 F.3d at 527 (stating that the "public [has] the right to experiment with and improve upon the patented subject matter").

Given that the patentee's exception "has not generated concerns about indefiniteness," *Pfaff*, 525 U.S. at 64, there is no reason why an infringer's experimental use defense, as envisioned by Justice Story, would not be as definite and workable as the patentee's exception. For example, the Federal Circuit has identified thirteen objective factors for determining if a patentee's public use is experimental, *see Electromotive Div. of Gen. Motors Corp. v. Transp. Sys. Div. of Gen. Elec. Co.*, 417 F.3d 1203, 1213 (Fed. Cir. 2005), and many of those same factors are equally relevant to an infringer's experimental use defense. *See* Andrew S. Baluch, Note, *Relating The Two Experimental Uses In Patent Law: Inventor's Negation And Infringer's Defense*, 87 B.U. L. REV. 213, 248 (2007) (identifying common factors). In both cases, experimental use is limited in scope to activities that are "primarily experimental and not commercial," and ends when the researcher knows that the invention, or improvement thereon, "will work for its intended purpose." *Id.* at 250-52 (citing cases). The follow-on researcher is then entitled to obtain a patent on the improvement, at which point the original patentee must cross-license with the latter to market the improved technology, and vice versa.[12]

In the context of "research tools" (including "DNA sequences" used as diagnostic tools), the National Institutes of Health ("NIH") have determined that applying the common law experimental use defense to such tools would be relatively straightforward. REPORT OF THE NATIONAL INSTITUTES OF HEALTH (NIH) WORKING GROUP ON RESEARCH TOOLS (1998). In particular, the NIH found there to be a "sensible distinction" between

> experimenting *on* a patented invention—i.e. using a patented invention to study the underlying technology or perhaps to invent around the patent, which is what the exemption covers—and experimenting *with* a patented invention to study something else, which the exemption does not cover.

Id. at app. D.

On a comparative note, the United Kingdom, Germany, Japan, China, Korea, Hong Kong, Canada, and many other countries have recognized an experimental use defense to patent infringement. *See* NATIONAL RESEARCH COUNCIL OF THE NATIONAL ACADEMIES OF SCIENCES (NAS), A PATENT SYSTEM FOR THE 21ST CENTURY 111-12 (Stephen A. Merrill, Richard C. Levin, and Mark B. Myers, eds., 2004). That this Court has not yet had an opportunity to consider and endorse Justice Story's defense has, some believe, provided "incentives for certain industries—specifically, those conducting commercial research on patented technologies hoping to obtain patentable improvements—to locate their research operations outside of the United States." John F. Duffy, *Harmony and Diversity in Global Patent Law*, 17 BERKELEY TECH. L.J. 685, 719 (2002).

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[12] *See, e.g.*, Robert P. Merges & Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839, 860-62 (1990) (explaining the concept of "blocking patents" where "one patentee has a broad patent on an invention and another has a narrower patent on some improved feature of that invention").

Thus, any pronouncement by this Court that patents "preempt" research aimed at studying or improving upon patented subject matter would mark a significant expansion of the traditional notion of infringement (and a significant narrowing of the traditional research exemption). Such a pronouncement, moreover, would disrupt settled expectations among university researchers who have long assumed that their basic research activities are shielded from infringement liability. *See* NATIONAL RESEARCH COUNCIL, at 109 (finding that a "research exception" had been "widely assumed, especially by academic investigators and research administrators, to shield scientific investigation at universities from lawsuits").

CONCLUSION

For the foregoing reasons, NanoBCA urges the Court to affirm the judgment of the court of appeals.

Respectfully Submitted,

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March 14, 2013

AMICUS
CURIAE
BRIEF

No. 12-398

In The
Supreme Court of the United States

◆

ASSOCIATION FOR
MOLECULAR PATHOLOGY, ET AL.,

Petitioners,

vs.

MYRIAD GENETICS, INC., ET AL.,

Respondents.

◆

On Writ Of Certiorari To The
United States Court Of Appeals
For The Federal Circuit

◆

BRIEF OF *AMICUS CURIAE* NATIONAL VENTURE CAPITAL ASSOCIATION IN SUPPORT OF RESPONDENTS

◆

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INTEREST OF *AMICUS CURIAE*[1]

The National Venture Capital Association (NVCA), with more than 400 members, is the venture community's preeminent trade association, advocating for policies that encourage innovation and reward long-term investment. NVCA's mission is to foster greater understanding of the importance of venture capital to the U.S. economy and support entrepreneurial activity and innovation. Venture capitalists are committed to funding America's most cutting-edge entrepreneurs, working closely with them to transform breakthrough ideas into emerging growth companies that put innovation in the hands of the public and drive U.S. job creation and economic growth. According to a 2011 IHS Global Insight study, venture-backed companies accounted for nearly 12 million jobs and $3.1 trillion in revenue in the United States in 2010.

NVCA and its members have an interest in preserving the patent rights that have created and continue to sustain the biotechnology industry, bringing life-changing technologies to market and spawning new high-growth companies.

◆

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[1] No counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amicus curiae* or their counsel made a monetary contribution intended to fund its preparation or submission. The parties have consented to the filing of this brief.

SUMMARY OF ARGUMENT

The venture community is the primary founder and funder of biotechnology in the United States, an industry which, year after year, provides hundreds of thousands of jobs, generates hundreds of billions of dollars in revenue, and makes available to the general public countless life-changing and life-saving innovations. *See* Ernst & Young, *Beyond Borders, Global Biotechnology Report* 27, 30 (2012) ("*Beyond Borders*"); Global Insight, *Venture Impact, The Economic Importance of Venture Capital-Backed Companies to the U.S. Economy* 9 (2011) ("*Venture Impact*"). Both Genentech and Amgen – companies that gave birth to modern biotechnology – were funded by venture capitalists. And today, venture capital firms supply nearly all of the capital for early-stage biotechnology companies.

Unlike in other technology sectors, start-up biotechnology companies are faced with long development timelines, unpredictable science, and uncertain industry adoption. In particular, the industry faces significant (with respect to both time and cost) regulatory hurdles. Venture capitalists are able to fund these not-yet-profitable emerging companies through the high-risk and high-cost development process because patent protection in the underlying technology makes possible potentially large rewards if a product can be brought to market. *See* Federal Trade Commission, *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy, A Report by the Federal Trade Commission*, Chp. 3, p. 1 (2003)

("FTC Report") ("Biotech representatives emphasized that patent protection is critical to attract the capital necessary to fund this high-risk investment."). Indeed, it was this Court's confirmation of Congress' broad view on patent eligibility as articulated in *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), that opened the door to patents covering isolated nucleic acids and the founding of modern biotechnology. FTC Report at Chp. 3, pp. 17-18. Soon after the *Chakrabarty* ruling, patents covering DNA encoding human growth hormone and erythropoietin issued, enabling venture capital investment in the early founders of modern biotechnology, Genentech and Amgen.

Since the success of Genentech and Amgen, venture capitalists have relied on the continuing issuance of these patents by the PTO, the PTO's consideration and confirmation of the patent eligibility of such inventions in its practice guidelines, and the enforcement of these patents by the courts to continue funding. Removing patent eligibility for isolated nucleic acid patents threatens an industry built on thirty years of precedent and industry practice. It not only forfeits the billions of dollars currently invested and hundreds of thousands of jobs created with the understanding that returns would be secured by nucleic acid patents, but also removes incentives for future investment in important new nucleic-acid based technologies, such as molecular diagnostics, gene therapies, agricultural food production, and alternative energy sources.

This Court has warned that "courts must be cautious before adopting changes that disrupt the settled expectations of the invention community." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002), *citing Warner-Jenkinson v. Hilton Davis Chem. Co.*, 520 U.S. 17, 18 (1997). The biotechnology industry's settled expectations regarding the patent eligibility of isolated nucleic acid is the foundation of the entire industry and continues to facilitate innovation and economic growth. Accordingly, this Court should confirm that isolated nucleic acids are patent eligible and affirm the Federal Circuit's ruling in favor of Respondents.

◆

ARGUMENT

I. THIS COURT'S PRECEDENT CAUTIONS AGAINST DISTURBING SETTLED EXPECTATIONS.

In the more than thirty years following this Court's recognition that § 101's legislative history intended "anything under the sun that is made by man" to be patent-eligible, both the legal and business community have relied on the understanding that inventions directed to isolated nucleic acids are patent-eligible under § 101. *See Chakrabarty*, 447 U.S. at 309 (citations omitted); *see also id.* at 316 (recognizing that "Congress employed broad general language in drafting § 101").

According to a 2003 Report by the Federal Trade Commission, the description of patent-eligible subject matter articulated in *Chakrabarty* "conveyed a broad sense of the potential scope of patents and, in particular provided a significant boost to the biotech industry." FTC Report at Chp. 1, p. 21 ("participants from the biotech industry generally credited the *Chakrabarty* decision as the beginning of their industry, without which genetic engineering would not have made nearly as much progress"); *see also id.* at Chp. 3, p.17 (reporting that participants stated that "*Chakrabarty* spurred significant growth in the biotech industry").

Consequently, in the thirty years since the *Chakrabarty* decision, the United States Patent and Trademark Office has granted tens of thousands of patents covering nucleic acids. *See* National Research Council of the National Academies, *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health* 101-02 (Stephen A. Merrill & Anne-Marie Mazza, 2006) ("*Reaping the Benefits*") ("From 1971 to 2006, approximately 33,000 issued nucleic acid patents have been identified."). Between 1995 and 2005 alone, over 6000 nucleic acid patents were issued, with an additional 7000 applications pending. *Id.* at 106. Over time, the PTO and courts have confirmed the validity of isolated DNA patents. *See e.g.* 66 Fed. Reg. 1092, 1093 (PTO Utility Examination Guidelines finding patenting of genes proper); *Amgen v. Chugai*, 927 F.2d 1200 (Fed. Cir. 1991) (first appellate decision that, in part, finds valid a claim to "purified and isolated DNA sequence . . . encoding human [protein]").

Most of these inventions are owned by private companies, many of which depend on these patents and patent applications to secure the capital necessary to develop and commercialize the underlying technology. *Reaping the Benefits* at 115; *see also e.g.* Federal Trade Commission, *Emerging Health Care Issues: Follow-on Biologic Drug Competition* v (2009) ("Patent protection enables biotechnology firms to increase their expected profits from investments in R&D, thus fostering innovation that would not occur without patents' exclusionary rights."); President's Council of Advisors on Science and Technology, *Priorities for Personalized Medicine* 21 (2008) ("PCAST *Priorities*") ("The ability to obtain strong intellectual property protection through patents has been, and will continue to be, essential for pharmaceutical and biotechnology companies to make the large, high-risk R&D investments required to develop novel medical products"). With this promise of patent protection, venture capitalists invested more than $35 billion in biotechnology between 2002 and 2011, with more than $4 billion invested in 2011 alone. *See Beyond Borders* at 44.

Reinterpreting § 101 now to exclude isolated nucleic acids from patent protection would disturb the investments and expectations established over more than three decades of practice. Nucleic acid patents gave rise to the modern biotechnology industry and continue to enable investment in emerging companies, bringing medical, agricultural and industrial innovations to market and promoting economic growth. This Court has "more than once cautioned that courts 'should not read into the patent laws limitations and conditions which the legislature has not expressed.'" *Bilski v. Kappos*, 561 U.S. ___, 130 S. Ct. 3128, 3228 (2010), *quoting Diamond v. Diehr*, 450 U.S. 175, 182 (1981); *see also Association for Molecular Pathology v. United States Patent and Trademark Office*, 653 F.3d 1329, 1374 (Fed. Cir. 2011) (Moore concurring in part) ("the judiciary is ill-suited to determine whether the claims at issue promote or inhibit science and useful arts in all but the clearest cases").

This warning is particularly noteworthy in the case of isolated nucleic acids, where Congress – though presented with the opportunity to do so – has declined to express any limitations on patent eligibility. For example, in 1993, the Life Patenting Moratorium Act was introduced in the Senate, proposing a two-year moratorium on the patenting of any "human tissue, fluid, cell, gene or gene sequence (genetically engineered or otherwise)." *See* S. 387, 103d Cong., 1st Sess. (1993). In 2007, the Genomic Research and Accessibility Act introduced in the House, contained a provision expressly precluding patenting of "a nucleotide sequence, or its functions or correlations." *See* H.R. 977, 110th Cong., 1st Sess. (2007). Both bills died in committee. Finally, in the recent enactment of the America Invents Act, the first major patent reform bill in fifty years, Congress instituted no limits on the patent eligibility of genes or other isolated nucleic acids. Instead, the legislative history reveals that Congress was aware that the Patent Office has already issued gene patents and was comfortable with legislation that would not affect that practice. *See* 157 Cong. Rec. E1177-04 (resubmitting testimony in connection with the AIA that stated "the U.S. Patent Office has already issued patents on genes . . . , but it has not issued patents on claims directed to human organisms, including human embryos and fetuses. My amendment would not affect the former, but would simply affirm the latter").

As this Court has recognized, "we must hesitate before departing from established general legal rules lest a new protective rule that seems to suit the needs of one field produce unforeseen results in another. And we must recognize the role of Congress in crafting more finely tailored rules where necessary." *Mayo Collaborative Serv. v. Prometheus Labs., Inc.*, 566 U.S. ___, 132 S. Ct. 1289, 1305 (2012); *see also Bilski*, 130 S. Ct. at 3229 (warning against "adopting categorical rules that might have wide-ranging and unforeseen impacts"). Not only have the rules here been long established, they have been relied upon to foster an industry that plays a significant role in furthering U.S. economic growth.

II. BIOTECHNOLOGY WOULD NOT EXIST WITHOUT PATENTS.

A. Biotechnology Is Marked By High Development Costs

Biotechnology covers a diverse collection of technologies, each of which capitalizes on the attributes of biological materials. *See* Biotechnology Industry Organization, *Guide to Biotechnology* 1 (2008) ("BIO Guide"). Thus, biotechnology reaches across many sectors, revolutionizing health care (*e.g.*, molecular diagnostics, biological therapeutics, vaccines, and pharmaceuticals), improving agriculture, and developing alternative energy sources. *See generally id.* at 32-69.

Regardless of the application, biotechnology products often take more than ten years and hundreds of millions of dollars to develop and bring to market. *Id.* at 77. Research and development is expensive and challenging. The underlying laboratory science can be laborious and unpredictable. Many sectors are subject to significant regulatory hurdles. *See e.g. id.* at 39-40 and 44 (describing regulatory process for therapeutics and agriculture). Even after securing regulatory approval, market success still requires industry adoption.

For example, bringing a molecular diagnostic to market requires laborious work with respect to the underlying science, including ensuring sufficient sample sizes, quality control in the underlying DNA sampling, a rigorous statistical approach to analyzing data, and a consistent standard across the industry. PCAST *Priorities* at 29-30. Moreover, the industry faces significant obstacles when navigating the regulatory environment. In particular, molecular diagnostics are subject to long, expensive clinical trials. In addition, the current regulatory system is not designed to accommodate new complex genomics-based diagnostics and for that reason can be even more costly to navigate. *Id.* at 41. And the regulatory requirements continue to increase year by year. There is also the practical necessity of convincing insurance companies, Medicare, and Medicaid to pay for these new tests, which requires robust evidence supporting the safety and efficacy of products. *Id.* at 45-48.

Development of new therapeutics is similarly mired by the cost of basic research, clinical trials, and post-approval testing. It is estimated that bringing a single biotechnology-related therapeutic to market takes 15 years and costs over $1.2 billion. *See* Henry Grabowski, *Follow-on Biologics, Data Exclusivity and the Balance Between Innovation and Competition*, 7 Nature Reviews Drug Discovery 479, 482 (2008) ("Grabowski"); BIO Guide at 38 ("It typically takes 10 to 15 years and an average of more than $800 million (including the cost of failures) to develop a new therapy."); *see also* PhRMA, *Key Industry and PhRMA Facts*, available at http://www.phrma.org/news-media/related-resources/key-industry-factsabout-phrma. Only an estimated 30 percent of biological therapeutics that make it as far as human trials succeed. Grabowski at 481.

B. Patents Enable Venture Capital Investment in Biotechnology

Most of the companies driving these new biotechnological innovations are small, having less than fifty employees. Without a significant source of capital, even when the technology is sound, these companies would run out of money before a product could ever be brought to market. BIO Guide at 77.

Thus, these companies simply would not exist without venture capital, often the only available source of funding for high-risk start-ups. *See* NVCA, *Patient Capital: How Venture Capital Investment Drives Revolutionary Medical Innovation* 7 (2007) ("*Patient Capital*") ("Because their capital needs are so large and their path to market so long and risky, it is difficult for life sciences startups to access bank financing or other more traditional sources of capital."). Indeed, venture capital funds almost all emerging biotechnology companies. *See* Hearing Before the Subcommittee on Courts and Competition Policy of the Committee on the Judiciary House of Representatives, *Biologics and Biosimilars: Balancing Incentives for Innovation* 182, 107th Cong., 1st Sess., Serial No. 111-73 (July 14, 2009) ("*Biologics* Hearing") (NVCA testimony that venture capital firms "supply nearly all of the capital for early-stage biotechnology companies"); *Patient Capital* at 3 ("Experts agree that virtually the entire biotechnology industry . . . would not exist without the support of the venture capital industry.").

To secure this much-needed venture capital investment, a company must have strong intellectual property in the form of patents. BIO Guide at 77 (noting that patents are "often the most important assets a biotech company has"); *Patient Capital* at 12 ("No other industry is as dependent on developing and protecting intellectual property as the life sciences industry."). In fact, the biotechnology industry would not exist but for patents. FTC Report at Chp. 3, pp. 1, 17-18 (reporting that "[b]iotechnology companies overwhelmingly underscored the importance of patents for attracting venture capital"). As reported by the Federal Trade Commission:

> Biotechnology innovation is heavily dependent on the patent rights that have been available for biotechnology inventions since 1980. Patents help firms to recover high, fixed R&D costs and are particularly useful in enabling biotechnology companies, which are generally small in size, to attract capital investment and to contract with other firms for commercial development of their inventions. This capital is critical for ongoing R&D, because product commercialization in the biotechnology industry is particularly time-consuming and expensive.

Id. at Chp. 3, p. 29. Patents provide the incentive for venture capitalists to invest in the "incredibly risky, illiquid, and long-term investments" required by biotechnology companies, over half of which fail. *Biologics* Hearing at 182. They are needed to "produce a return that is much higher than you can get from less risky investments" by "provid[ing] a period of exclusivity with respect to the manufacture, use, or sale of the product." *Id.*; *Reaping the Benefits* at 20; *see also* Claude Barfield, et al., *Biotechnology and the Patent System* 11 (2007) ("Investors believe that in order for the biotechnology sector to succeed, it is critical that biotechnology firms be able to obtain and enforce strong patents.").

Thus, strong patent protection, including for isolated nucleic acids, is imperative to secure the investment that drives continued biotechnological innovation.

III. ISOLATED NUCLEIC ACID PATENTS ARE THE FOUNDATION OF MODERN BIOTECHNOLOGY.

The importance of patents, and isolated nucleic acid patents in particular, to venture capital financing and the resulting realization of new revolutionary technologies is not merely theoretical. In fact, it was nucleic acid technology that enabled venture capital investment in Genentech, the company often credited with the birth of the biotechnology industry. *See e.g.* BIO Guide at 2 (crediting emergence of biotechnology on development of recombinant DNA technology by co-founder of Genentech); *see generally* Cynthia Robbins-Roth, *From Alchemy to IPO: The Business of Biotechnology* (2000) ("*Alchemy*").

Genentech was founded in 1976 based on recombinant DNA technology developed by scientists at

Stanford University and the University of California, San Francisco. *Alchemy* at 14. The scientists applied for patents covering this new DNA-based technology. *Id.* at 15. Based on this technology, the company was founded with the help of the venture capital firm Kleiner, Perkins, Caufield & Byers. *Id.* Initial funding lasted nine months, during which time Genentech worked on its "proof of concept," cloning genes for insulin and human growth hormone out of Kleiner Perkins' offices. *Id.* at 16. The next year, Kleiner Perkins invested another round and Genentech secured additional financing by selling rights to its technology. *Id.* at 25. It is estimated that isolation of the human insulin gene – rights to which were sold to Eli Lilly – took over $100 million and 1000 human years of labor. By 1979, Genentech expanded its technology and filed a patent application covering its technique for cloning human growth hormone. *See* Ser. No. 55,126, U.S. Patent No. 4,342,832. This patent application eventually gave rise to a patent claiming "a DNA molecule consisting of DNA encoding . . . human growth hormone." U.S. Patent No. 4,898,830.

Armed with its patent applications and the proof of concept made possible through Kleiner Perkin's investment, Genentech went public in October 1980, raising over $35 million. *Alchemy* at 20. In 1985, Genentech marketed its first drug, Protropin®, secured by its human growth hormone DNA patent. *Id.* at 29; *see also* http://www.omnilegalgroup.com/GeneWars.pdf at 17 n.xxxix (noting that HGH was marketed as Protropin® and is covered by U.S. Patent No. 4,898,830). By 1998, revenues for Protropin® reached $214 million. *Alchemy* at 28.

Amgen is another company that experienced a similar success story. Formed in 1980 by a group of scientists and investors, Amgen secured $19 million in financing from venture capital firms and two major corporations. *Alchemy* at 34. By the mid-1980s Amgen had five genetically engineered drugs undergoing testing but its work with erythropoietin was most promising. Erythropoietin (EPO) is a hormone that promotes red blood cell production. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1203 (Fed. Cir. 1991). In a race with six other companies to isolate the EPO gene sequence, by 1984, Amgen had applied for a patent claiming "an isolated and purified DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin." Ser. No. 675,298, U.S. Patent No. 4,703,008; *see Alchemy* at 39. Following the issuance of its EPO patent in 1987, Amgen received FDA approval for its Epogen product in 1989 and has since successfully enforced its patent against competitors to secure market exclusivity. *Amgen*, 927 F.3d at 1219 (affirming validity of EPO DNA sequence claims and finding of infringement). To date, Epogen remains one of Amgen's leading products. Facilitating venture investment in these emerging biotechnology companies through patents covering isolated nucleic acids not only ensures that the public will enjoy the benefits of new breakthrough innovations, it brings about far-reaching downstream economic benefits as well.

Genentech and Amgen's success, secured by patents covering isolated nucleic acids, spurred the growth of an industry. Biotechnology is now an industry with over $58 billion in annual revenue. *Beyond Borders* at 27. In 2010, venture-backed biotechnology companies realized $161 million in revenue and accounted for 400,000 jobs. *Venture Impact* at 9.

While venture capital investments equal less than 0.2 percent of the US GDP, annually, VC-backed companies have generated revenue equal to 21 percent of the US GDP. *Venture Impact* at 2. Venture-backed companies constituted 11 percent of private sector jobs in 2010. *Id.* at 3. The biopharmaceutical industry, for instance, has an enormous ripple effect throughout the economy. The Milken Institute projects that for every job within biopharmaceuticals, an additional 6.7 jobs are created in other sectors of the economy. *Patient Capital* at 8, *citing* Milken Institute, *Biopharmaceutical Industry Contributions to State and U.S. Economies* (2004).

A reduction of these jobs and the revenues generated by eliminating venture-backed companies will have significant unintended consequences on the economy. Indeed, venture-backed companies have been sustaining the economy, outperforming the total overall economy in 2009-2010. *Venture Impact* at 2. Where overall revenues decreased 1.5 percent, venture-backed revenue grew 1.6 percent, totaling $3.1 trillion in 2010 (10% of total U.S. sales). *Id.* at 3.

Thus, the current system which has been relied upon for over thirty years has supported steady economic growth and support for new technologies and emerging industries.

IV. THE BIOTECHNOLOGY INDUSTRY CONTINUES TO RELY ON PATENTS COVERING ISOLATED NUCLEIC ACIDS.

The industry's reliance on isolated nucleic acid patents is not just historical. Nucleic acid patents continue to play an important role in bringing biotechnological advancements to market.

Patents on isolated DNA molecules continue to support investment in new revolutionary technologies.

4s3 Bioscience is a venture-backed bio-therapeutics company developing therapies for genetic neuromuscular diseases. Founded in 2007, 4s3 Bioscience has two pending patent applications with claims directed to a "nucleic acid construct containing a nucleotide sequence that encodes a MBNL [MTMI] polypeptide." *See* U.S. Patent Pub. Nos. 2010/0111977 and 2012/0213760. With these patent applications, 4s3 Bioscience secured $20 million in Series A financing in March 2012 to fund further development of antibody technology that provides targeted and active delivery of proteins, enzymes, and other molecules to skeletal muscle. *See* http://www.alopexx.com/press_release/4s3-bioscience-inc-secures-20m-in-series-a-financing/.

As seen with the 4s3 Bioscience technology, nucleic acid patents are important to the continued development of protein therapeutics and the emerging field of gene therapy. Gene therapy uses DNA or related nucleic acid molecules to treat diseases by supplying a patient with a replacement, non-defective gene. Development of this technology has the potential to save lives through the treatment of cancers and immunodeficiency diseases. *See* BIO Guide at 34.

Denying patent protection for human DNA also puts patents covering isolated nucleic acids of other organisms at risk. Patent protection for bacterial or plant nucleic acids has significant impact on the development of agricultural, industrial, and environmental products. Funding for continued research and development into the genomes of bacteria and algae, for example, has the potential to lead to great innovation in alternative energies and potential sources for biofuels. For example, cellulosic ethanol technologies, which can process non-food plant materials (*e.g.*, grass, wood, and crop waste) into ethanol, rely heavily on cellulose and hemicellulase genes isolated from microorganisms that break down the materials. The many issued patents that are directed to isolated DNA coding for these cellulases and hemicellulases have been critical in driving rapid innovation in this industry. And patents for isolated plant DNA can improve agricultural practices, decrease the cost of food, and help address the global food supply. *See* BIO Guide at 53.

The potential applications of nucleic acid technology, involving human DNA as well as DNA of other organisms, is limitless. Stifling such innovation into new and unexplored territories will lead to unforeseen and undesired consequences. Biotechnology has historically benefitted and brought life-changing innovation based upon the understanding that isolated nucleic acids are patent-eligible. Changing that practice now will halt the type of progress and advancements that the industry and society has experienced over the last thirty years.

◆

CONCLUSION

For the foregoing reasons, the judgment of the Court of Appeals should be affirmed.

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AMICUS CURIAE BRIEF

Supreme Court, U.S.
FILED
JAN 30 2013
OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

ASSOCIATION FOR MOLECULAR
PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT
OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF *AMICI CURIAE* OF THE NATIONAL WOMEN'S HEALTH NETWORK, REPRODUCTIVE HEALTH TECHNOLOGIES PROJECT, DISABILITY RIGHTS LEGAL CENTER, FORWARD TOGETHER, THE CENTER FOR GENETICS AND SOCIETY, THE PRO-CHOICE ALLIANCE FOR RESPONSIBLE RESEARCH, ALLIANCE FOR HUMANE BIOTECHNOLOGY, G. MICHAEL ROYBAL, MD, MPH, AND ANNE L. PETERS, MD IN SUPPORT OF PETITIONERS

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INTEREST OF *AMICI CURIAE*[1]

Amici Curiae advocate in the area of women's health and the delivery of healthcare in a manner which prioritizes social justice. They have unique expertise regarding policy issues concerning women's health and health disparities for women and their families who are socio-economically disadvantaged and underserved, or of particular ethnic and racial backgrounds. *Amici Curiae* understand the implications of genetic technologies for women's health and use this knowledge to educate community based organizations and individuals, and to advocate for public policies concerning genetic technologies that are just and equitable. *Amici Curiae* also include physicians/ researchers who work within our burdened healthcare system. Experts in clinical care and treatment of underserved populations they recognize the importance of accessibility and quality of genetic technologies for preventative medicine, treatments, and potential cures.

The continued allowance of the patenting of the BRCA 1/2 genes is a deep concern of *Amici Curiae. Amici* understand that these patents are for molecules which are the embodiment of important scientific information and knowledge regarding the human genome. *Amici* recognize that the preemption of knowledge regarding these genes, which indicate a susceptibility to breast and ovarian cancer limits access to quality genetic testing and inhibits innovative work in research and treatments for these serious conditions, with resultant detrimental effects for the health of the women, communities and patients they serve, particularly those most in need of the benefits of current and future genetic technologies.

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[1] The parties have consented to the filing of this brief and letters of consent to the filing were lodged with the Clerk of the Court. No counsel for a party authored this brief in whole or part, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amici curiae* and their members or their counsel made a monetary contribution to its preparation or submission.

Amicus Curiae **The National Women's Health Network** improves the health of all women by developing and promoting a critical analysis of health issues in order to affect policy and support consumer decision-making. The Network has particular expertise in women's health issues as a result of their research and evaluation of emerging drugs, devices and treatments and their impact on women's health. The Network aspires to a health care system that is guided by social justice and reflects the needs of diverse women, including the support of individual decision-making by providing evidence-based information free from corporate influence.

Amicus Curiae **Reproductive Health Technologies Project (RHTP)** a national non-profit organization advocating on behalf of women to enable access to the safest and most effective methods for the protection of their health, the RHTP is a powerful vehicle for public education and policy development surrounding health technologies. Bringing together experts, using solid science and clinical data to influence political outcomes, and seeking consensus among diverse communities, the RHTP ensures that new technologies are developed and introduced with appropriate safeguards, a well-informed consumer constituency and broad-based public support.

Amicus Curiae **Disability Rights Legal Center (DRLC)** champions the rights of people with disabilities through education, advocacy, and litigation. Together with the Loyola University School of Law at Los Angeles, they direct a joint program, the **Cancer Legal Resource Center (CLRC)**. Founded in 1997, the CLRC has provided free information and resources on cancer-related legal issues to cancer survivors, caregivers, health care professionals, employers, and others coping with cancer, serving over 310,000 people through conferences, seminars, workshops, education and outreach programs, and other cancer community activities. To this end, the CLRC runs a free and confidential national Telephone Assistance Line that assists individuals with cancer and genetic-related legal issues, including the costs of testing, insurance coverage, employment, and access to health care and government benefits.

Amicus Curiae **Forward Together** is a nonprofit community-based multi-racial organization that engages in grass-roots action and training community leaders, working in communities of color to ensure that women and adolescents have the information they need to improve their own health status, and believing in policy that enables *all* people to have the economic, social, and political power and resources necessary for decision-making regarding their bodies.

Amicus Curiae **The Center for Genetics and Society (CGS)** is a nonprofit information and public affairs organization working to encourage responsible uses and effective societal governance of genetic, reproductive and biomedical technologies. CGS works with a growing network of civil society leaders, health professionals, scientists, and others who share a commitment to advancing the public interest in the development of just and equitable policies regarding human biotechnologies.

Amicus Curiae **The Pro-Choice Alliance for Responsible Research (PCARR)** is a coalition of reproductive rights and justice advocates, bioethicists, academics, and community leaders working together to promote accountability, safety and social justice in biomedical research from a women's rights perspective. PCARR believes that justice, safety, and dignity for women must be paramount in public policy and private practice in emerging biotechnologies. Since 2004, PCARR has been providing research and legal analysis to policymakers and consumers, and engaging with administrative agencies to ensure that women's health outcomes are protected in the implementation of new biotechnologies.

Amicus Curiae **Alliance for Humane Biotechnology (AHB)** is a non-profit association that conducts outreach and education on the social and environmental impacts of human biotechnologies. Scholars, students and activists, the AHB publishes and speaks about commercialization issues concerning both human beings and the natural environment, working for a culture of science that places the health and welfare of people above financial interests.

Amicus Curiae **G. Michael Roybal, MD, MPH** is the Medical Director of the Roybal Comprehensive Health Center (CHC), established to address the inequity of communities and individuals without access to affordable healthcare. Dr. Roybal has spent his career working with the Department of Health Services for Los Angeles County, focusing on healthcare redesign and reform in an attempt to improve healthcare delivery for underserved populations.

Amicus Curiae **Anne L. Peters, MD**, is the Director of the Diabetes Clinic at the Roybal Comprehensive Health Center (CHC) and a Professor at the USC Keck School of Medicine. An internationally known expert in the field of treatment for diabetes, she has received numerous grants to improve health environments and reduce obesity rates in underserved populations. Her work at the CHC provides over 80,000 yearly patient visits, mostly for the uninsured. A similar program she developed is situated at five additional safety-net sites in Los Angeles County.

SUMMARY OF ARGUMENT

The question in the case at bar asks whether human genes, which include the BRCA 1/2 genes, are patentable. *Association for Molecular Pathology, et al, v. Myriad Genetics, Inc., et al.*, 133 S. Ct. 694, 184 L. Ed. 2d 496 (2012). *Amici* argue that vital policy considerations and precedents of the Court impel this Court to decide that these genes are for phenomena of nature, patent-ineligible exceptions to the statutory categories of patentable subject matter per 35 U.S.C. § 101.

Amici advocates, educators, and clinicians, who work to improve the health of women and their families and to eliminate disparities in the delivery and quality of healthcare, understand that the continued allowance of the patenting of human genes, specifically the BRCA 1/2 genes at issue in this case has a deleterious effect on the health and well-being of women and their families, and a disproportionately harmful effect on those who are socio-economically disadvantaged and underserved or are of particular racial and ethnic backgrounds, unable to benefit from current advancements in genetic technologies. The work of *Amici* is impeded as these patents preclude and limit access to the most current and accurate scientific and biomedical knowledge regarding the human genome and the BRCA 1/2 genes. *Amici* understand that progress and innovation in research and treatment for breast and ovarian cancer is inhibited by Myriad's patents on these human genes.

Fundamental to this understanding is the recognition that the isolated DNA/cDNA molecules of the BRCA 1/2 genes revealing a susceptibility to breast and ovarian cancer are structures that are the embodiment of important scientific information and knowledge regarding the human genome. The specific patent claims on these molecules are broad, general, and sweeping claims which preempt, restrict, and limit access to these basic tools necessary for scientific work. As a result, these exclusionary patents privatize and monopolize the use of this knowledge, which necessarily produces grave harms for the health of women and their families.

The exclusionary patents restrict basic biomedical research and inhibit research and development of alternative testing methods for breast and ovarian cancer. The accessibility of genetic tests as well as the quality of testing methods is limited by the existence of Myriad's patents. The progress of biomedical science is significantly slowed as the development of innovative new methods in the field of personalized medicine for diagnostics and treatments of breast and ovarian cancers is inhibited as a result of the continued patenting of the BRCA 1/2 genes. The health of socio-economically disadvantaged and underserved women and their families and women from particular ethnic or racial backgrounds is disproportionately harmed as a result of these patents which limit both access to and the quality of testing for these groups. *Amici* argue that these impediments to the advancement of science which create grave harms for the health of women and the communities they serve should be an important consideration for this Court in deciding the present question.

Amici also argue that recent decisions of this Court considering 35 U.S.C. § 101 subject matter eligibility warn against patents on phenomena of nature whose preemption create impediments to the advancement and progress of science, *see, e.g.*, *Mayo v. Prometheus*, 132 S. Ct. 1289, 182 L. Ed. 2d 321 (2012), and that the claims at issue are similarly patent-ineligible phenomena, laws and products of nature, whose preemption from use impedes scientific and biomedical innovation. The claims to the isolated DNA/cDNA do not rest upon inventive concepts, rather the claims are for laws of nature which simply describe natural relationships and pre-existing scientific principles, and products of nature, molecules that despite the technical processes of isolation are not markedly different from the DNA, the BRCA 1/2 genes in their natural state.

Analogous to recent decisions of this Court, Myriad's patent claims tie up too much of the future use of fundamental information and knowledge of the human genome regarding the BRCA 1/2 genes. The resultant inhibition of innovation and progress in biomedical research and healthcare treatment for breast and ovarian cancer is not justified by Myriad's original identification of the claims at issue.

For these reasons this Court should find Myriad's claims ineligible for patent protection according to 35 U.S.C. § 101.

ARGUMENT

I. Patents on the BRCA 1/2 Genes Create Grave Harms for the Health of Women and Their Families.

Amici recognize that the continued allowance of these previously granted patents on the BRCA 1/2 genes have increasingly negative implications for the health of women and their families. In 2012, 226,870 new cases of invasive breast cancer and 57,650 cases of in-situ breast cancer, with a resultant 39,920 deaths, and 22,280 cases of ovarian cancer with a resultant 15, 500 deaths were estimated. American Cancer Society, Cancer Facts and Figures, 2011-2012, [hereinafter, "ACS"]. While the average woman in this country has around a 12%-13% risk of developing breast cancer in her lifetime, women with BRCA mutations face a cumulative risk of between 50%-80% for breast cancer and a 20%-50% cumulative risk of ovarian cancer. *Ass'n for Molecular Pathology v. United States PTO*, 689 F.3d 1303, 1314 (Fed. Cir. 2012)

Testing for BRCA mutations is critical for decisions regarding clinical care, including surgical and therapeutic options. *Id.* at 18-19. Patents which exclude the scientific and medical community from the use of important information and scientific knowledge, specifically the embodied information of the BRCA 1/2 genes, necessarily inhibit progress and innovation in breast and ovarian cancer biomedical research and treatment, with resultant harmful effects for the health of woman and their families.

The agreed upon facts of the case define the fundamental nature of a human gene, the ordering of the nucleotides of the isolated DNA/cDNA molecules of the BRCA 1/2 genes as the physical embodiment of genetic information and scientific principles. *Ass'n for Molecular Pathology v. United States PTO*, 702 F. Supp. 2d 181, 193 (S.D.N.Y. 2010). Myriad's specific patent claims illustrate the reach of these patents which cover all isolated forms of the naturally occurring genes, whether previously identified or not. The patents are exclusive grants given for all uses of the informational content embodied in the genes' chemical structures, thus access to basic scientific principles for scientists, researchers, clinicians and patients is denied, with resulting restrictions on biomedical research and the development of treatments for breast and ovarian cancer.

The scope of Myriad's claims on the isolated DNA/cDNA of the BRCA 1/2 genes inhibit and restrict basic biomedical research and research and development of alternative genetic testing methods for breast and ovarian cancer. The patents restrict access to genetic testing and negatively affect the quality of genetic tests. The patents also inhibit future innovation in the development of personalized medicine by creating uncertainty and high transactions costs for the implementation of new diagnostic techniques such as whole genome sequencing (WGS) and whole exome sequencing, as well as creating impediments for the development of new and targeted treatments, dependent upon knowledge regarding the BRCA 1/2 genes. Socio-economically disadvantaged and underserved women and their families and woman of particular ethnic and racial backgrounds are disproportionately harmed as a result of limited access to and the diminished quality of

BRCA 1/2 testing. Restrictions on the use of the isolated DNA/cDNA molecules of the BRCA 1/2 genes create grave harms for the health of women and their families.

A. Claims to Isolated DNA/cDNA of the BRCA 1/2 Genes are for the Physical Embodiment of Information whose Preemption Restricts Access to and the Use of Vital Scientific Principles and Biomedical Knowledge.

DNA is a chemical molecule composed of four standard repeating chemical units, adenine, thymine, cytosine and quinine (aka, A, T, C, G) known as nucleotides, or bases. *Ass'n. for Molecular Pathology v. United States PTO*, 702 F. Supp.2d 181, 193 (S.D.N.Y. 2010). The ordering of these bases is described as nucleotide sequences, DNA sequences or gene sequences. *Id.* at 194. Gene sequences constitute biological information, describing the structural and chemical properties of a particular DNA molecule that is the cellular "blueprint" for the productions of proteins, and are of a double nature: they are both "chemical substances of molecules as well as physical carriers of information, i.e., where the actual biological function of this information is coding for proteins." *Id.* at 194, 228, citing Strauss Decl. at P 20.

For patenting purposes, "...since information is encoded as molecular structure, the information is only useful when embodied in such structures." *See*, Dan Burk, *The Problem of Process in Biotechnology*, 43 Hous. L. Rev. 561, 582-87 (2006). "The interest is not in the string of 'letters' of the sequence, but ...the molecules that are the conduit for information transfer." *Id.* at 586-87.

The sole content of Myriad's isolated DNA/cDNA claims are these informational structures, the embodiment of the specified nucleotide sequences of the BRCA 1/2 genes. *See*, e.g. claims 2, 5, 6, 7 of U. S. Patent No.5,747,282; claims 1, 6, 7 of U. S. Patent No. 5,837,492. *Ass'n.*, 702 F. Supp.2d at 212. Claim 1 of the '282 patent is for "1) An isolated DNA coding for a BRCA-1 polypeptide[protein], said polypeptide having the amino acid sequence set forth in SEQ ID NO: 2." U.S. Patent No. 5,747,282 col. 154 ll.56-58 (filed June 7, 1995). This is an extremely broad patent as multiple DNA sequences "correspond to the nucleotide sequence claimed in this claim." *Ass'n.*,702 F. Supp. 2d at 212.

Other claims are equally illustrative of the reach and scope of Myriad's patents. Claim 5 of the '282 patent covers any isolated DNAs "having at least 15 nucleotides" of the BRCA 1 gene, thus the claim covers the entire BRCA 1/2 genes. The patents cover both known and unknown mutations for increased susceptibility to breast and ovarian cancer, e.g., Claim 6 of the '492 patent is "directed to any DNA nucleotide encoding any mutant BRCA 2 protein that is associated with breast cancer," including all possible mutations and variations found within those genes.

The claimed ordering of the nucleotide sequences is informational content identical to the informational content found in the native DNA source, despite minor structural changes made to the isolated molecule itself. As a result, the utility of the isolated DNA molecules as biotechnological tools "relies on their ability to selectively bind to native or isolated BRCA 1/2 DNA molecules." *Id* at 197. Even though differences exist in its physical form, derived from mRNA, a cDNA molecule (e.g., Claim 2 of the '282 patent) represents "an exact copy of one of the protein coding sequences encoded by the original genomic DNA," *id.* at 198, which is similarly being claimed for its embodied, replicated informational content.

These patents give Myriad the right to exclude anyone from using the DNA of the BRCA 1/2 genes, or copies of these genes outside the human body. The patents restrict all research and clinical testing of the BRCA 1/2 genes. Unlike patents on new drugs, no one can "invent around" Myriad's patents as one cannot invent a molecule of DNA which encodes the protein which embodies the genetic information of an individual's BRCA 1/2 genes. The preemptive effects of these patents inhibit progress and innovation in biomedical research and treatments for breast and ovarian cancer.

B. Myriad's Patents Inhibit and Restrict Biomedical Research and Research and Development of Alternative Testing Methods for the BRCA 1/2 Genes.

"Empirical evidence demonstrates...a real fear on behalf of clinical laboratory directors and researchers... that patent holders can and will prevent them from conducting their research." Richard Gold and Julia Carbone, *Myriad Genetics: In the Eye of the Policy Storm*, 12 Genetics in Medicine S39 (2010) [hereinafter "Gold"]. Clinical laboratories decide not to develop new or improved genetic tests in light of patents, where 53% of surveyed laboratory directors did not develop alternative tests. *See e.g.*, Mildred K. Cho, et al., *Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services*, 5 J. Molecular Diagnostics 3, 5 (2003). Researchers have stated that Myriad prevented the development of improved BRCA 1/2 tests, the ability to assess the quality of Myriad's tests, and the development of treatments for breast and ovarian cancer. Gold, *supra* at S44.

Although Myriad claims it does not enforce its patents against researchers, Myriad has never publicly stated this policy in a written form, one which acts as a basis for the actions of others and which includes activities Myriad would consider as infringing. *See Secretary's Advisory Committee on Genetics, Health & Society: Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests*, 4-2010, at A26-27 [hereinafter "*Report*"]. Thus, "[a]mbiguity may itself stifle basic or clinical research as researchers either avoid the work altogether or are wary of public reporting results." *Id.* at A-27.

Prior to the issuance of Myriad's patents, researchers and scientists were studying BRCA genes, but ceased doing so when alerted to potential infringement liability. Laboratories reported nine instances of Myriad having enforced their BRCA patents, *id.* at 7, citing Cho, *supra* at 3-5, and two laboratories received cease and desist letters, including one at the University of Pennsylvania, the Genetics Diagnostics Laboratory (GDL). Gold, *supra* at S44. Scientists expressed concerns about contributing their research results on the BRCA genes to public databases as the basis for invoking patent infringement claims, and one researcher from the University of Alberta was specifically told not to contribute new mutations based upon this assumption. *Id.*

As a result of exclusive testing, Myriad accumulated significant amounts of data relating to previously unknown mutations, known as variations of unknown significance (VUS), but did not investigate these ambiguous results. *Statement Submitted by Dr. Marc C. Grodman to the House Judiciary Subcommittee on Courts, the Internet, and Intellectual Property* (Oct. 25, 2007). Myriad also denied access to this important information. In November 2004 they stopped contributing this data to the NIH open access Breast Cancer Information Core (BIC) mutation database, and ceased publishing information regarding the VUS in peer-reviewed literature, creating a major impediment to significant research. John Conley, Dan Vorhaus, Robert Cook- Deegan: Genomics Law Report, March 1, 2011: *How Will Myriad Respond to the Next Generation of BRCA Testing?*, available at http://www.genomicslawreport.com/index.php/2011/03/01/ how-will-myriad-respond-to-t.

C. Myriad's Patents Restrict Access to and Diminish the Quality of Genetic Tests for the BRCA 1/2 Genes.

Patent monopolies on human genes eliminate competition, likely resulting in higher prices, diminished patient access, and decreased quality in genetic testing. *See*, Roger D. Klein, MD, JD, *Gene Patents and Personalized Medicine, 2012, American Society of Clinical Oncology* at 82 [hereinafter "Klein"]. Generally, patients have greater access to genetic tests within competitive markets. Andrew S. Robertson, *The Role of DNA Patents in Genetic Test Innovation and Access*, 9 Nw. J. Tech. & Intell. Prop. 377 at 397-98.

Based upon its BRCA patents, Myriad is the sole provider of genetic testing for breast and ovarian cancer in the United States and has stopped other laboratories from conducting testing on the genes. *Report* at 40. Identifying and providing alternative testing methods by researchers other than Myriad is prohibited, restricting access to numerous testing methods. Robert Cook-Deegan, Subhashini Chandrasekharan & Misha Angrist, *The Dangers of Diagnostic Monopolies*, 458 Nature 405 (2009). For example, as Myriad has "little incentive to analyze samples other than blood samples," *House Judiciary Subcommittee on Courts, the Internet and Intellectual Property*, Washington D.C.: 2007, Statement of Wendy Chung, their decision not to use one alternative testing method (paraffin-embedded tissue) has "hampered availability of that type of testing in instances where it might be clinically useful." *Id.*

Alternative methods are ones which might be more cost-effective or efficient: "When compared to the most cost-effective mutation detection strategy analyzed...the average cost per mutation using the Myriad approach was five times as high," more than tests that had been developed and were used in Europe. *Report* at A-27. European methods do not necessarily insist upon initially testing the whole gene sequence as in the BRCA test, therefore Myriad has unilaterally established the "standard of care" in the United States; arguably precluding the use of potentially more efficient testing methods. *Id.* at A-28.

Myriad's patents deny the ability of patients to access a confirmatory test from a different laboratory, equivalent to a physician's independent second opinion. *Report* at 44. Patients for whom Myriad's initial test produced inconclusive results may be forced to accept those results, relying only upon Myriad's data. This lack of information greatly impairs the decision-making of both a patient and their physician. "The ability to obtain a confirmatory test from a second laboratory is important because genetic test results can have implications for major medical decisions, such as whether to have a mastectomy or surgical removal of the ovaries." *Id.*

The quality of genetic testing for the BRCA 1/2 genes is diminished as a result of exclusive patenting practices. Any research resulting in a commercial or clinical service infringes Myriad's patents, notably "... the assessment of technology by third parties, e.g. to evaluate a test for sensitivity, specificity, or positive predictive value." Ozdemir, et al, *Shifting Emphasis from Pharmacogenomics to Theragnostics*, Nature Biotechnology, Vol. 24 No. 8 (2006).

Testing for the BRCA genes is limited to Myriad's laboratories, thus the test's accuracy in identifying mutations in the BRCA genes (analytical validity) and predicting a patient's risk for breast or ovarian cancer (clinical validity) cannot be determined by clinical geneticists outside of Myriad's purview without risking infringement liability. A study by non-clinical researchers found 10-20% of false negatives in patients at high risk. Walsh T., Casadei S, Coat KH et al., *Spectrum of Mutations in BRCA 1, BRCA 2, CHEK and TP53 in Families at High Risk of Breast Cancer*, 295 JAMA 1379 (2006) [hereinafter "Walsh"]. However since clinical geneticists cannot participate in similar studies, the effectiveness of Myriad's test cannot be validated.

Myriad's patent-based restrictions on the development of quality testing have produced serious harms. The 2006 study used an alternative molecular testing method and found that Myriad's test missed up to 12% of large genomic deletions or duplications, also known as "Large Genomic Rearrangements" (LGR). *Id.* Because this more accurate method requires the use of Myriad's patented gene sequence, the performance of the test would be considered an infringement.

Following the publication relating to their flawed BRAC Analysis test, Myriad developed an additional test, the BRAC Analysis Rearrangement Test (BART), which is separately offered for the detection of these missed mutations. K.M. Shannon et al., *Which Individuals Undergoing BRCA Analysis Need BART Testing?* 204 Cancer Genetics 416 (2011) [hereinafter "Shannon"]. Testing is based upon Myriad's criteria, a personal and family history that selects for individuals with a high pre-test probability (> 30%) of carrying a BRCA 1/2 mutation. *Id.* at 416. One genetic counselor noted that she had rarely mentioned the BART test to women undergoing testing, as information given to her from Myriad led her to believe that the additional BART mutations were "extremely rare among women…without an extremely strong family history of breast and ovarian cancer." Elizabeth Cohen, *When Breast Cancer Tests Gets it Wrong*, available at http://www.cnn.com/2011/10/27/health/brca-genetic-testing-ep/index.html. [hereinafter, "Cohen"]. Nonetheless subsequent studies showed that a substantial number of women have the BART mutations without a strong family history, *see, e.g.*, Shannon, *supra* at 418, suggesting the possibility of a woman developing breast and/or ovarian cancer as a result of missed preventative tests.

Myriad's patents also prevent labs from offering more rapid, cost-effective, and accurate testing methods such as genomic capture and massive parallel sequencing for multiple breast and ovarian cancer susceptibility genes:

> "Currently, the vast majority of genetic testing in the United States for inherited mutations in the BRCA 1 and BRCA 2 is done via a single company at a cost of ~$4000 for a non-comprehensive test that is complemented by an additional test to identify gene rearrangements. Far less clinical genetic testing for ovarian cancer risk is carried out for the other tumor suppressor genes. Targeted capture and massive parallel sequencing accurately identify mutations of all classes in all tumor suppressor genes in a single test. There is an increasing discrepancy between the falling cost of genomic sequencing and the current high cost of clinical gene by gene testing. As more cancer susceptibility genes are identified, it is not economically sustainable to assess risk by sequentially assessing individual genes, given that any one gene is mutant in only a small percentage of cases." Tom Walsh et al, *Mutations in 12 Genes for Inherited Ovarian, Fallopian Tube, and Peritoneal Carcinoma Identified by Massively Parallel Sequencing*, 108 Proc. Nat'l. Sci. U. S. 17857, 18036 (2011).

Thus, with Myriad's technology, if their initial tests are negative then testing for other breast or ovarian cancer genes is done selectively, based upon specific family or personal histories or physical examinations.

These extra tests cost thousands more dollars beyond the costs of both Myriad's standard ($3,300) and BART ($700.00) tests. However, with new methods, "it is possible to identify mutations in the 21 known breast and ovarian cancer genes in one sample for a cost…less than $1500.00… with further bar-coding and indexing strategies the costs could be reduced to less than $500.00 per sample." Walsh, Lee, Casadei, Thorton, Stray, Pennil, Nord, Mandell, Swisher, and Mary-Claire King; PNAS Early Edition, *Detection of Inherited Mutations for Breast and Ovarian Cancer Using Genomic Capture and Massive Parallel Sequencing*, www.pnas.org/cg/10.1073/pnas [hereinafter "King"].

These new testing methods are also more accurate than Myriad's tests. A new method of evaluating multiple genes in addition to BRCA 1/2 "identified a wide range of mutations in a variety of genes in 100% of [] test cases with zero spurious mutations called." *Id.* Six large deletions and duplications were identified which could have been missed by Myriad's standard test. *Id.* "By allowing comprehensive parallel testing of multiple cancer susceptibility genes, we will be able to confidently identify the fraction of women with breast and ovarian cancer who carry a germline alteration in a cancer susceptibility allele and the characteristics of the tumors of patients' inherited mutations in various genes." *Id.* Such tests, however, cannot be done on the BRCA 1/2 gene sequences without infringing Myriad's patents.

D. Myriad's Patents Inhibit Future Innovation in Personalized Medicine.

Myriad's patents inhibit future innovation in the area of personalized medicine, whose development rests upon genotype-phenotype associations (e.g. BRCA 1/2 mutations and the susceptibility to breast and ovarian cancer). *See*, Klein, *supra* at 81. New methods of testing for these associations, able to detect millions of genetic variations and mutations in thousands of genes or even the entire genome will guide treatments, drug dosages and prevention for numerous diseases. However, "If we are to enter the next stage of personalized medicine, we cannot do so by parceling out information-genomes do not work that way, pleiotropy...doesn't stop at the lines drawn by the USPTO." Zachary Russ, *The Holes in Whole Genome Sequencing, Genetic Engineering & Biotechnology News*, available at: http:// www.genengnews.com/blog-biotech/the-holes-in-whole-genome-sequencing/676. Myriad's patents create uncertainty for the implementation of new diagnostic technologies and inhibit the development and delivery of new therapies.

The findings that approximately 20% of human genes are referenced in patent claims, the ownership of which is spread over a large number of assignees, have significant implications for the future use of new technologies including multi-plex testing, massive parallel sequencing, and whole genome sequencing (WGS).

"Patent thickets, blocking patents, royalty stacking, and high transactions costs" threaten the use of these next generation innovations in genetic testing. *Report* at 50-51. Fearing liability, laboratories using multiplex tests are not reporting results to patients or sending clinicians the results of tests involving patent protected genes. *Id.*

Myriad's patents on isolated DNA/cDNA create uncertainty where questions of liability are complicated by varying interpretations of claim language. Myriad's attorney stated that "without an isolating procedure directed at gauging BRCA mutations whole genome sequencing would not infringe Myriad's patents." Turna Ray, *At Appeals Hearing, Myriad Outlines Stance on BRCA IP Rights for Whole-Genome Sequencing*, April 4, 2010, available at: http://www.genomeweb.com/dxpgx/appeals-hearing-myraid-outlines-stance-brca-ip-rights. However he did not define "isolating." The interpretation of the term will be a factor in determining the question of patent infringement in the context of WGS. Scholar Robert Cook-Deegan questioned the limiting effect of the term isolated: "How do you do DNA sequencing without some purification step? Even nanopore or scanning-tunneling (electro-machining) means isolating some piece of DNA…That's an 'isolated' molecule you're measuring. It's a meaningless distinction." *Id.*

Thus, illustrative of high transaction costs, WGS industries may need to examine specific patent claims for "all or many of the thousands of human genome sequences subject to patent protection." Dan Vorhaus and John Conley, *Genomics Law Report, Whole Genome Sequencing and Gene Patents Coexist (For Now)*, August 11, 2009, available at: http://www.genomicslawreport.com/index.php/2009/08/11/whole-genome- sequencingand. The patents potentially inhibit the use of WGS in assessing for risk or existence of disease, and thus, patient care. National Society of Genetic Counselors, *Position Statement of Human Gene Patents*, available at: http://www.nsgc.org/Advocacy/PositionStatements/tabid/107/Default.aspx (2010).

Exome sequencing, targeted sequencing restricted to the protein-coding subset of human genes, is based upon an "enrichment of targeted DNA regions by hybridization with probes." Patricia F. Dimond, Ph.D., *Exome Sequencing Finds Sweet Spot Between Whole-Genome and Targeted Sequencing*, Genetic Engineering & Biotechnology News, available at: http://www.genengnews.com/key wordsandtools/print/3/25217/. The technique's costs relating to data collection, storage and analysis are significantly less than those in WGS techniques, and also lead to the discovery of highly pertinent variants. *Id.* However, "exome sequencing is more likely to face IP issues…because gene patents typically cover methods that would specifically target or enrich for the gene." Monica Heger, *Interpretation Remains Key Challenges in Clinical Sequencing; Patents May Impede Return of Results.* Genome Web, June 27, 2012. Available at: http://www.genomeweb.com/print/1096581.

The potential for infringement involving the use of these new methods could "slow some promising clinical technologies." Subhashini Chandrasekharan and Robert Cook Deegan, *Gene Patents and Personalized Medicine, what Lies Ahead?* Genome Medicine, 2009, 1:92. For example, holdout problems might result when drug manufacturers creating targeted therapies "do not own the underlying molecular pathological relationships." Klein, *supra* at 82.

Myriad's patents implicate these concerns. Numerous cancer patients, as many as 50% with inherited BRCA 1/2 mutations have a negative family history and do not qualify for testing according to Myriad's criteria. King *supra* at 4. However, the development of specific treatments, inhibitors which effectively kill BRCA 1/2 mutated carcinomas having therapeutic as well as preventive applications, necessitates an increased need for identifying BRCA 1/2 mutations in women with breast and ovarian cancer through testing, which is restricted by Myriad's exclusive test on the patented sequences. *Id.*

The development of one treatment option, an inhibitor known as PARP for individuals with BRCA 1/2 associated cancers has been impeded as a result of Myriad's patents. Susan Domcheck, et al., *Challenges to the Development of New Agents for Molecularly Defined Patient Subsets: Lessons From BRCA 1/2 Associated Breast Cancer*, Journal of Clinical Oncology, Vol 29, No 32 (November 10) 2011, pp. 4224-4226. "A targeted therapeutic agent would presumably lead to widespread BRCA testing at diagnosis to identify those who would benefit...and thus would additionally expand the potential number of patients who are eligible for treatment." *Id.* at 4225. However,

> "...the United States Food and Drug Administration requires a companion diagnostic test that will define the population of interest before approval is granted for an agent directed toward that population. There is presently no US Food and Drug Administratively-approved diagnostic test for determining germline BRCA status, although mutation results have been used for more than a decade to make major decisions about preventive surgeries. The regulatory approval of such a diagnostic is hampered by ongoing uncertainty with respect to the status of the BRCA testing patent held by Myriad Genetics...." *Id.*

Thus, the subsequent development and delivery of an important treatment option has been impeded as a result of Myriad's patents.

E. The Health of Socio-Economically Disadvantaged and Underserved Women and their Families and Women of Particular Racial and Ethnic Backgrounds is Disproportionately Harmed as a Result of Myriad's Patents on the BRCA 1/2 Genes.

Socio-economically disadvantaged and underserved women and their families and women of particular ethnic and racial groups are disproportionately harmed by Myriad's exclusive and broad patents. One study reported ethnicity-specific mutation prevalence estimates ranging from 9.4% to 15.6%, with pooled estimates of 12.6% for women of European (Western and Central) ancestry and 14.1% for all women of non-European ancestry (Latin American, African, Asian, Native American, and Middle Eastern). Hall, et al., *BRCA 1 and BRCA 2 Mutations in Women of Different Ethnicities Undergoing Testing for Hereditary Breast Cancer*, Cancer, Volume 115, Issue 10, pages 2222-2233, 15 May 2009. However, despite similar mutation prevalence, "Testing volumes are disproportionately low among women from non-European ancestries and likely reflect the complex social, economic, and cultural factors that govern healthcare access and use." *Id.*

Disparities in the cancer burden among ethnic and racial minorities largely "reflect obstacles to receiving health care services" including early detection, and lowered socio-economic status is the overriding factor.

See, ACS at 43. There is less access to genetic testing for underserved ethnic and racial minorities than for those in the white population. Armstrong K., Micco E., Carney A., et al., *Racial Differences in the Use of BRCA 1/2 Testing Among Women with a Family History of Breast or Ovarian Cancer,* 293 JAMA 1729 (2005). E.g., African-American women are 78% less likely to use genetic BRCA testing than white women, and although less diagnosed, they are more likely to die from the disease. *Id.* Financial restraints including the lack of insurance, underinsurance, and incomplete Medicare/Medicaid reimbursements result in underserved populations having lesser access than whites to genetic testing services and is a significant barrier to comprehensive cancer care. Michael J. Hall, Olufunmilayo I. Olopade, *Confronting Genetic Testing Disparities*, 293 JAMA 1783 (2005).

The price of Myriad's test is necessarily prohibitive. "Myriad, as a monopolist, maximizes its profit through price discrimination in which it charges the highest price to those women who most value the test." *Report* at A-32. Thus, access to Myriad's test is severely limited for those without insurance, and even for the insured, the coverage for BRCA testing has been inconsistent and reimbursement is limited to those at high risk. *Report* at 37-38.

Myriad's policies regarding the supplemental BART test has had deleterious effects for the economically disadvantaged. The BART test, originally expected to be offered as part of its original test, is indicated for all patients with histories suggesting BRCA 1/2 mutations, however if a patient does not meet Myriad's defined criteria, the test is an additional $700.00. Shannon, *supra* at 420. While some insurers reimburse the additional costs, many do not, and others consider BART to be an investigational test, excluded from coverage. *Id.*

Thus, the test is difficult to access for many women as a result of the added cost. One genetic counselor notes, "We know we're missing women out there with BART mutations because they can't afford to pay. If you miss just one BART mutation, that woman could be in danger, and so could her mother, her sisters, and her other relatives," Cohen, *supra.*, including her daughters.

Myriad's patents also affect the quality of the tests for women of particular ethnic and racial backgrounds. Large genomic deletions or duplications, known as large genetic rearrangements (LGR) will be found in approximately 12% of patients with both breast cancer and a "severe" family history who test negative for the BRCA genes, and studies have advocated testing for LGR in specific ethnic populations. Shannon *supra* at 418. Data from Myriad suggests that these LGR BRCA mutations are over-represented and account for a larger percentage of mutations than previously thought in some populations, e.g., 20% of Latina women, suggesting a need for the additional BART test to be included in the standard BRCA analysis for all patients. *An Open Letter to Myriad Genetics*, Friday, July 22, 2011, available at http://yalecancergeneticcounseling.blogspot.com/2011_07_11 archive.html.

The concern for quality testing for minority populations is implicated in the assessment of risk for breast and ovarian cancers, as the lack of access to Myriad's tests for underserved racial and ethnic populations diminishes the quality of the test itself. Michael J. Hall, Olufunmilayo I. Olopade, *Disparities in Genetic Testing: Thinking Outside the BRCA Box*, 24 J. Clin Oncol 2197 (2006) [hereinafter "Hall"].

Models to assess risk used in BRCA testing need accurate estimates of the prevalence in specific populations to estimate probabilities in particularly high risk genotypes. *Id.* However the prevalence of Ashkenazi groups in testing shows a 10 fold increased prevalence in this group compared with estimates for the remaining U.S. population. *Id.* Without accurate estimates of mutation prevalence in minority subgroups, the reliability of these models is compromised. *Id.*

Myriad's patents on the embodied information of the BRCA 1/2 genes inhibit important scientific work in biomedical research and treatment for breast and ovarian cancer, with serious and harmful implications for the health of women, particularly socio-economically disadvantaged and underserved women or women of particular racial or ethnic backgrounds. As such Myriad's claims to the BRCA 1/2 genes should be considered ineligible for patent protection.

II. Isolated DNA/cDNA Molecules are Patent-Ineligible Phenomena of Nature. The Claims Do not Rest on Inventive Concepts and are Laws and Products of Nature, Whose Preemption Inhibits Scientific and Biomedical Progress and Innovation.

"Laws of Nature, natural phenomenon, and abstract ideas are not patentable subject matter under § 101 of the Patent Act." *Mayo*, 132 S. Ct. at 1293, citing *Diamond v.*

Diehr, 450 U. S. 175, 185, 101 S. Ct. 1048, 67 L. Ed. 2d 155 (1980). Additionally, "phenomenon of nature, though just discovered... are not patentable, as they are the basic tools of scientific and technical work." *Id.*, citing *Gottschalk v. Benson*, 409 U. S. 63, 67, 93 S. Ct. 253, 34 L. Ed. 2d 273 (1972).

Deciding the patent eligibility of a claim to a diagnostic process, this Court recently clarified the law/product of nature doctrine by explaining what necessitates turning a patent-ineligible law of nature into a patentable application of that law. *Mayo v. Prometheus*, 132 S. Ct. 1289, 182 L. Ed. 2d 321 (2012). The nature of the medical diagnostic method at issue was described as a relationship, a law of nature, *id.*, 132 S. Ct. at 1297, as nothing of significance had been added to the underlying natural phenomenon to make it a patentable application of that law, i.e., the claim did not rest on an inventive concept. *Id.*, at 1297-1300. Significantly, *Mayo* considered the preemptive effect of the patent relevant to their conclusion that the resultant inhibition of innovation rendered the process ineligible for patent protection. *Id.*at 1302.

Mayo's analysis is equally applicable to a composition claim. Myriad's patents on the BRCA 1/2 genes are for phenomena of nature analogous to the claimed relationship in *Mayo*. Lacking an inventive concept, nothing of significance has been added to the law/product of nature itself to render it patent-eligible. Myriad's claims to the isolated DNA/cDNA molecules of those genes simply describe natural phenomena, relationships which are laws of nature and pre-existing scientific principles. The molecules themselves are products of nature which are not markedly different whether inside or outside the human body. The preemption of these phenomena of nature inhibits progress and innovation in scientific and biomedical research and treatments.

A. Myriad's Claims to Isolated DNA/cDNA do not Contain Inventive Concepts

Processes using a natural law must also contain an inventive concept so that the patent is "significantly more than a patent upon the natural law itself." *Mayo*, 132 S. Ct. at 1294. Mayo considered whether a process for measuring the relationship between concentrations of metabolites in the blood and a likelihood that a certain dosage of drug would prove effective or cause harm, was patent-eligible subject matter. *Id.*, 132 S. Ct. at 1296. Despite administering a drug to trigger the manifestation of the relationship, the relationship existed apart from any human action and was an entirely natural process. *Id.* at 1296-97. The claims did not rest upon inventive concepts as nothing in the steps of the process added anything of significance to the law of nature itself. *Id.*, at 1298. The process was essentially for the underlying relationship, a patent-ineligible law of nature. *Id.*, at 1302.

The steps in *Mayo's* claimed process -- administering, determining, and a wherein step -- simply told doctors to gather data and draw inferences in light of the correlations. *Id.*, at 1298. The steps were well understood, routine, conventional activity already engaged in by the scientific community. *Id.* The claims were not transformative and did not make a claimed law of nature a patentable application of that law. *Id.*

Claims to isolated DNA/cDNA molecules do not rest on inventive concepts. The claim terms indicating isolation or synthesis do not add anything of significance to render these laws and products of nature patent-eligible. "Isolated" simply denotes "a nucleic acid...which is substantially separated from other cellular components which naturally accompany a native human sequence." *Ass'n*, 702 F. Supp at 213, n.30. Having been derived from mRNA, a synthesized cDNA molecule represents an exact copy of one of the protein coding sequences encoded by the original genomic DNA. *Id.* citing Leonard Decl. P 75.

Well-established laboratory techniques are used in these processes for isolating the claimed molecules from their cellular environment. *Id.*, at 198. DNA sequencing processes used to determine the ordering of the nucleotides within a DNA molecule are well known techniques understood and routinely performed by scientists skilled in molecular biology. *Id.*, at 200. These conventional activities add nothing to the phenomenon of nature itself. Thus, these claims to phenomena of nature do not rest on inventive concepts.

B. Isolated DNA/cDNA Molecules of the BRCA 1/2 Genes are Laws of Nature.

The process in *Mayo* claimed a correlation, primarily a relationship between concentrations of metabolites in the blood and the likelihood that a certain dosage of drug would prove effective or cause harm: "The relation is a consequence of the ways in which thiopurine compounds are metabolized by the body-entirely natural processes." *Mayo*, 132 S.Ct. at 1297. Despite the human action of administering a drug to manifest the relation, "a patent that simply describes that relation sets forth a natural law." *Id.*, at 1298.

Isolated DNA/cDNA molecules are patent-ineligible laws of nature, analogous to the claimed process of *Mayo*. Myriad's claimed molecules of the BRCA 1/2 genes are the embodiment of important information and pre-existing scientific principles; both their structure and function encodes the relationship between a DNA molecule and a protein. The structure of the nucleotides in the molecule enables the instructions for the building of proteins in the human body, or within identical and synthesized DNA. The patent claims disclose the sequential information embodied by the molecules, the ordering of the nucleotides.

This ordering of the chemical bases, the arrangement of nucleotides is, analogous to the law of nature in *Mayo*, a relationship, an entirely natural phenomenon. The ordering is a pre-determined relationship, a correlation that reveals a genetic susceptibility to breast and ovarian cancers in the BRCA 1/2 genes, a pre-existing scientific principle. The relationship remains unchanged apart from the human action of isolation or synthesis. The claims "simply describe the relations" between the order of the nucleotides and their resulting chemical, structural, and functional content and merely "point out a set of facts that exist in the world…." *Mayo v. Prometheus*, 2011 U.S. Trans. LEXIS 76 *39, *43 (2011).

The Court in *Mayo* also determined whether the steps involved in the questioned process were "sufficient to transform unpatentable natural correlations into patentable applications," *Mayo*, 132 S. Ct. at 1298, by looking at cases where processes "embodied the equivalent of natural laws." *Id.* The process in *Diehr* embodied the Arrenhius equation to cure rubber; an algorithm in *Flook* was used to adjust alarm limits; and *Benson* used a mathematical principle to convert numbers on a computer, *id.*; all were recognized as underlying laws of nature, unsuitable subject matter for patent protection.

Myriad's claims to the isolated DNA/ cDNA molecules are analogous. The ordering or arrangement of chemical base pairs embodied as an isolated molecule is an equation, a formula for the production of proteins; the mathematical ordering or arrangement of chemical base pairs an algorithm which dictates biological processes. The fixed nature of the relationship of the nucleotides arranged in the BRCA 1/2 genes which reveal a susceptibility to breast or ovarian cancer is a mathematical principle. As such, Myriad's claims on isolated DNA/cDNA are laws of nature, exceptions to the categories of patentable subject matter described in 35 U.S.C. § 101.

C. Isolated DNA/cDNA Molecules of the BRCA 1/2 Genes are Products of Nature.

Products of nature are exceptions to the statutory categories of patentable subject matter under § 101. *Diamond v. Chakrabarty*, 447 U. S. 303, 100 S. Ct. 2204, 65 L. Ed. 2d 144 (1980). In two separate opinions resting upon identical rationales the Federal Circuit erred in its determination that claims to isolated DNA/cDNA molecules are patent eligible. See, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 653 F.3d 1329, 1351 (Fed.Cir. 2011); *Ass'n for Molecular Pathology v. Myriad Genetics, et al.*, 2012 U. S. App, LEXIS 17679 at 56-61.

In its latest decision, the Federal Circuit disregarded *Mayo* and relied solely on the test established in *Diamond v. Chakrabarty*, 447 U. S. 303, 100 S. Ct. 2204, 65 L. Ed. 2d 144 (1980) to determine that the claimed molecules were "markedly different" from what existed in nature, and thus patent-eligible. *Ass'n*, 2012 U. S. App, LEXIS 17679 at 56-61. What distinguished Chakrabarty's invention, a bioengineered oil degrading bacterium, from the invention in *Funk Brothers*, a mixture of cultures of root bacteria capable of inoculating the seeds of certain leguminous plants "...were "markedly different characteristics from any...found in nature." *Id.*, citing *Chakrabarty*, 447 U.S. at 310.

The Federal Circuit reasoned that while DNA molecules exist in the body (native DNA) as part of a "large structural complex," (i.e., part of a chromosome), isolated DNA is "a free- standing portion of a larger natural DNA molecule" which had been cleaved (i.e., had covalent bonds in its backbone chemically severed, or synthesized to consist of just a fraction of a naturally occurring DNA molecule). *Id.*, at 61-62. Solely as a result of this cleavage or synthesis, the isolated DNA/cDNA was declared a distinctive chemical identity, and thus "markedly different" from patent-ineligible products of nature. *Id.*

However, this minute change in physical structure does not make the isolated or synthesized molecules, "markedly different" from their native state or endow them with a distinctive identity Rather, the Federal Circuit dismissed established biological truths regarding the functionality of the molecules, finding their informational content irrelevant: "We recognize the biologists may think of molecules in terms of their uses, but genes are in fact materials having a chemical nature and, as such, are best described in patents by their structures rather than their functions." *Id.*

This bifurcation of the gene as a hierarchy of structural and functional components denies the fundamental nature, or "identity" of the subject matter at issue. Unlike other chemicals, the isolated DNA/cDNA molecules describe and embody the nucleotide sequences which direct the proteins, cells and organs which make up the body. This biological function is the defining and identical characteristic of DNA/cDNA both before and after isolation or synthesis, and thus, these molecules are not markedly different from their native state. In fact, if these isolated or synthesized molecules had a truly distinctive chemical identity or were markedly different from what exists in nature their applications in research and diagnostics could not use the natural biological characteristics of DNA sequences to code for a protein and to anneal to its complementary nucleotide sequence. Products of nature, they "...serve the ends nature originally provided." *Funk Bros. Seed Co v. Kalo Inoculant Co.*, 333 U. S. 127, 131, 68 S. Ct. 440, L. Ed. 588 (1948).

D. Myriad's Patents Impede Progress and Innovation in Biomedical Science.

A patent is a right which allows the exclusion of others from making, or using the patented invention. 35 U.S.C. § 271(a) (2000). This Court has repeatedly emphasized the concern that "patent law not inhibit further discovery by improperly tying up the future use of laws of nature," as this might impede, rather than promote innovation. *Mayo*, 132 S. Ct. at 1301.

This Court's precedents, "...warn us against upholding patents that too broadly preempt the use of a natural law." *Id.*, citing *O'Reilly v. Morse*, 56 U.S. 62, 14 L. Ed. 601 (1854). Examples include general claims for underlying scientific principles, *id*, abstract and sweeping claims to a mathematical formula which covered both known and unknown uses of that formula, *id.*, citing *Benson*, 409 U.S. at 67, 93 S. Ct. 253, 34 L. Ed. 2d 273, a concept involving business transactions which precluded the use of its approach in all fields, *id.*, citing *Bilski v. Kappos*, 130 S. Ct. 3218, 177 L. Ed. 2d 792 (2010), and a formula that could be preempted from use in a broad range of possible uses. *Id.*, citing *Parker v. Flook*, 437 U. S. 584, 586, 98 S.Ct. 2522, 57 L. Ed. 2d 451 (1978).

Mayo recognized that patenting basic scientific tools posed a danger for future innovation, particularly if more future innovation was foreclosed than justified by the underlying discovery. *Id.*, at 1301. Although the claimed law of nature in *Mayo* was narrow, these concerns were implicated, affecting the ability of doctors to determine treatment options and threatening the development of more refined treatment recommendations which would combine features of the correlation with later discoveries involving aspects of human physiology and biology. *Id.*, at 1302. This preemption of future uses of laws of nature reinforced this Court's conclusion that the processes were not patent eligible. *Id.*

Myriad's patents on isolated DNA/cDNA "too broadly preempt natural laws." They are "general," preempting all uses of fundamental principles of molecular biology and genetics. The claims are "sweeping" covering both "known and unknown uses" of the embodied information of the BRCA 1/2 genes, preempting this knowledge from all fields of biomedical research and healthcare, including a broad range of potential uses for diagnosing and treating breast and ovarian cancer.

The practical implications of this preemption inhibit progress and innovation. Because Myriad's patents give them a monopoly on genetic testing for breast and ovarian cancer in the United States, like the physicians in *Mayo* unable to change their treatment options, physicians in our country cannot give second opinions regarding a diagnosis for the disease. Like the physicians in *Mayo* unable to refine their treatment methods, physicians treating breast and ovarian cancer are unable to refine their treatment methods because basic biomedical research and research and the development of alternative genetic testing methods have been restricted by Myriad's monopolies on the BRCA 1/2 genes. These patents have limited scientific discoveries and will continue to inhibit innovation.

The monopolization of the BRCA 1/2 genes, laws and products of nature, tie up too much of their future use. The resultant inhibition of future discoveries in biomedical research and healthcare treatment is not justified by Myriad's original discovery. Myriad's claims isolated DNA/cDNA of the BRCA 1/2 genes are patent-ineligible laws and products of nature whose preemption impedes innovation and progress in science and medicine.

CONCLUSION

The patenting of the isolated DNA/cDNA molecules of the BRCA 1/2 human genes creates grave harms for the health of all women and their families. Additionally, these molecules are phenomena of nature, patent ineligible exceptions to the categories of patentable subject matter, per 35 U.S.C., § 101. For the foregoing reasons *Amici* respectfully ask that the Federal Circuit's decision regarding the patent eligibility of the human genes at issue be reversed.

Respectfully submitted,

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CURIAE
BRIEF

No. 12-398

Supreme Court, U.S.
FILED

MAR 14 2013

OFFICE OF THE CLERK

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE NEW YORK INTELLECTUAL PROPERTY LAW ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENTS

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INTEREST OF *AMICUS CURIAE*

The New York Intellectual Property Law Association ("NYIPLA" or "Association") respectfully submits this brief *amicus curiae* in support of Respondents, Myriad Genetics, Inc. *et al.* ("Myriad").[1]

The arguments set forth herein were approved on March 12, 2013 by an absolute majority of the officers and members of the Board of Directors of the NYIPLA, including any officers or directors who did not vote for any reason, including recusal, but do not necessarily reflect the views of a majority of the members of the Association, or of the law or corporate firms with which those members are associated. After reasonable investigation, the NYIPLA believes that no officer or director or member of the Committee on *Amicus* Briefs who voted in favor of filing this brief, nor any attorney associated with any such officer, director or committee member in any law or corporate firm, represents a party in this litigation. Some officers, directors, committee members or associated attorneys may represent entities, including other *amici curiae*, which have an interest in other matters which may be affected by the outcome of this litigation.

The NYIPLA is a professional association of approximately 1,300 attorneys whose interests and practices lie in the area of patent, trademark, copyright, trade secret and other intellectual property law. The Association's members include a diverse array of attorneys specializing in patent law, from in-house counsel for businesses that own, enforce and challenge patents, to attorneys in private practice who represent inventors in various proceedings before the United States Patent and Trademark Office ("PTO").

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[1] 1. Petitioners consented to the filing of *amicus curiae* briefs in support of either party or neither party in a docket entry dated January 2, 2013, and Respondents consented to this filing in correspondence dated February 27, 2013. Pursuant to Sup. Ct. R. 37.6, no counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than NYIPLA, its members, or its counsel made a monetary contribution to its preparation or submission.

A substantial percentage of the Association's member attorneys participate actively in patent litigation, representing both patent owners and accused infringers. The NYIPLA's members also frequently engage in patent licensing matters on their clients' behalf, representing both patent licensors and licensees.

The entities served by the Association's members include inventors, entrepreneurs, venture capitalists, businesses, universities, and industry and trade associations. Many of these entities are involved in research, patenting, financing and other commercial activity relating to biotechnology generally, and a significant number in such activities relating to the important narrower areas of genomic research and the modification of genetic material.

The NYIPLA's members and their respective clients have a strong interest in the issues presented by this case because their day-to-day activities depend on the consistently-applied and longstanding broad scope of patent-eligible subject matter under the Patent Act in general. Because of the vital and increasing importance of biotechnology and the modification of genetic material to the economy, moreover, the NYIPLA and its members have a particularly strong interest in ensuring that their reasonable expectation that those principles continue to be consistently applied in those important areas.[2]

The NYIPLA's members demonstrably have a strong interest in ensuring that the Court does not disturb the current, clearly-defined framework governing the patent eligibility and patentability of inventions relating to modified genetic material that Congress enacted and that this Court has previously construed. In view of the enormous strides made in the related science of genomics since the initial discovery of Watson and Crick in 1953, it is equally important to the Association that this Court confirm that application of 35 U.S.C. § 101 to the technology of genetic modification should not unduly be conflated with considerations of patentability under Sections 102, 103 and 112.

STATEMENT

1. *Amicus* respectfully submits that the question presented—"Are human genes patentable?"—is inextricably intertwined with issues that this Court already has considered and settled.

Since this Court has confirmed at least twice within the past 33 years that compositions of matter and manufactures derived from living things are patentable under Sections 102, 103 and 112 of the Patent Act, *a fortiori* they necessarily are patent-eligible under Section 101. *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 147 (2001) (concluding that a "composition of matter" . . . . includes living things"); *Diamond v. Chakrabarty*, 447 U.S. 303, 313 (1980) (concluding that Congress has "recognized that the relevant distinction was not between living and inanimate things, but between products of nature, whether living or not, and human-made inventions").

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[2] The technological and financial importance of claims to modified living genetic material were highlighted before this Court during oral argument on February 19, 2013 in *Bowman v. Monsanto Co., et al.* (No. 11-796) ("*Bowman v. Monsanto*"). Indeed, the significance of those issues to its members led the NYIPLA's Board to authorize the filing of a brief *amicus curiae* in that proceeding. *See* Brief for the New York Intellectual Property Law Association as *Amicus Curiae* in Support of Respondents, *Bowman v. Monsanto Co.* (No. 11-796) (filed January 22, 2013).

Indeed, the holding of *Chakrabarty* must be read to include a determination that a composition of matter or manufacture is patent-eligible when it incorporates naturally-occurring hereditary units analogous to human "genes." 447 U.S. at 305 n.1, 306, 307.

Moreover, the crucial distinction this Court drew in *Chakrabarty*, "between products of nature, whether living or not, and human-made inventions," logically must be read to govern the patent eligibility of the inventions that Myriad claimed. *Id.* at 313. On the one hand, "human genes" as they are found in the human body are (and should be) ineligible for patent protection. On the other, extracted and isolated deoxyribonucleic acid ("DNA") obtained by human intervention from a naturally-occurring source must be deemed patent-eligible. *Id.* at 309 (noting that "Congress intended statutory subject matter to include anything under the sun that is made by man.") (internal quotation marks and citations omitted).

Myriad's claims cover patent-eligible subject matter under Section 101. If those claims satisfy all other statutory requirements including, importantly, Sections

102, 103 and 112, then Myriad is entitled to exclude others during the term of the patent (1) from making or using the claimed inventions for commercial benefit, and (2) from selling modified genetic material. But the claims cover and would therefore exclude only isolated and extracted DNA that would not exist in the first place without human intervention.

Enforcement of Myriad's claims will not prevent or preempt the use of any human genetic material as found in the human body. Given the broad statutory grant which protects "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof," subject matter that would not exist without human intervention should be found patent-eligible under Section 101 of the Patent Act. 35 U.S.C. § 101; *Chakrabarty*, *supra*; *J.E.M.*, *supra*.

2. DNA is a chemical compound that exists in nature as two separate chains, bound together to form a double helix structure. Pet. App. 14a-15a. Each chain is a polymer formed from a set of four monomeric nucleotides—adenine ("A"), guanine ("G"), cytosine ("C") and thymine ("T")—each unique by virtue of a different nitrogen-containing base. Those bases have the unique property of selectively pairing to other bases according to a simple rule: A always pairs with T, and C always pairs with G. One strand of double-helical DNA will be the complement of the other, a structure determined and stabilized by base-pairing between those two antiparallel strands.

In humans, DNA is organized into twenty-three pairs of chromosomes. Pet. App. 18a-20a. Each chromosome contains a single double-helical molecule formed from millions of nucleotide monomers. Naturally-occurring human chromosomal DNA is therefore a specific single chemical, accurately identifiable only by its precise ordered nucleotide sequence. Different DNA sequences may have different functions that may, as in the BRCA1 and BRCA2 genes in this case, correlate with potential susceptibility to certain diseases in the organism that expresses them. Pet. App. 20a-21a.

In addition to its specificity, chromosomal DNA is also a special chemical because, *inter alia*: (i) specific nucleotide sequences in a DNA molecule may be attributed to and responsible for a particular cellular function, and (ii) those sequences, and their attendant functions, are heritable from generation to generation.

A "gene" is an organizing principle that accounts for the various functional properties exhibited by chromosomal DNA. Pet. App. 13a-17a. One important cellular function of genes is to encode proteins through a dual process of DNA transcription to form ribonucleic acid ("RNA"), and RNA translation to form proteins—the "central dogma" of molecular biology. For this function, a "gene" is defined spatially as that discrete region of chromosomal DNA responsible for the synthesis of a particular protein. This region is not necessarily continuous, however, as exons, the portions of the "gene" encoding the protein are flanked and interrupted by introns, or non-coding sequences. Other non-coding sequences are responsible for a gene's *in vivo* function by modulating its transcription rate. Those non-coding sequences may serve vitally important and dynamic control functions within the gene and between different genes. Therefore, a "gene" as a functional entity reflects the complex participation of both coding and non-coding DNA sequences as they are found in naturally-occurring chromosomal DNA.

3. The claims-in-suit do not cover "human genes." For example, claim 1 of U.S. Patent No. 5,747,282 ("the '282 patent") is a representative claim that recites:

> 1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.

'282 patent, col. 153 ll. 55-58. The term "isolated" in the claim is significant because it immediately identifies a DNA molecule within the scope of the claim as distinct from a DNA molecule that might exist naturally in a human based on its separation from chromosomal DNA. *See* '282 patent, col. 19 ll. 8-12 (defining an "isolated" DNA as "one which is substantially separated from other cellular components which naturally accompany a native human sequence").[3]

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[3] On their face, the claims at issue do not involve "human genes" as in the question presented, and also avoid the potential written description issues involved in simply claiming a "gene" without further elaboration on the sequences covered. For example, in a claim directed to a "gene comprising SEQ ID NO:1,"

> [a] determination of what the claim as a whole covers may result in a conclusion *that specific structures* such as a promoter, a coding region, or other elements are included. Although all genes encompassed by this claim share the characteristic of comprising SEQ ID NO:1, there may be insufficient description of those specific structures (*e.g.*, promoters, enhancers, coding regions, and other regulatory elements) which are also included.

Manual Pat. Examining Proc. ("MPEP") § 2163 (emphasis supplied).

In another application, the "isolated DNA" of the representative claim above could correspond only to the exons—that subset of the full gene that specifically encodes the BRCA1 polypeptide. For example, claim 2 of the '282 patent recites:

> 2. The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1.

'282 patent, col. 153 ll. 59-60. SEQ ID NO:1 corresponds to the nucleotide sequence excluding the non-coding introns and flanking portions. As discussed above, those excluded sequences are prominent features of the naturally-occurring gene that almost certainly play a role in the normal functioning of that DNA sequence *in vivo*. SEQ ID NO:1 represents a different chemical species, a complementary DNA ("cDNA") molecule that, as with the isolated DNA molecule of claim 1, does not exist in nature and can only be created by purposeful human activity. Pet. App. 267a-269a.

4. It is significant that the question presented asks whether human genes are "patentable." This Court has recognized that the Patent Act require distinct "Conditions for Patentability" for validly issued patents. *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. __, 131 S.Ct. 2238, 2242 (2011) (recognizing that 35 U.S.C. § 282(b)(2) provides a defense that a patent is invalid for failing to meet any ground specified as a condition for patentability); *Diamond v. Diehr*, 450 U.S. 175, 189 (1981) (noting that "[s]pecific conditions for patentability follow [Section 101] and § 102 covers in detail the conditions relating to novelty"); *id.* at 191 & n.13 (noting Congress' deliberate division between statutory subject matter in Section 101 and other conditions for patentability in Section 102); *see*

also H.R. Rep. No. 1923, 82d Cong., 2d Sess., 6 (1952) (stating that a "person may have 'invented' a machine or a manufacture, which may include anything under the sun that is made by man, but it is not necessarily patentable under section 101 unless the conditions of the title are fulfilled").

Patentability refers to a holistic analysis of *all* conditions for patentability, including, *inter alia*, novelty under 35 U.S.C. § 102, non-obviousness under 35 U.S.C. § 103, and adequate disclosure and definiteness required by 35 U.S.C. § 112. Indeed, determining whether human genes may be patented at all—*i.e.*, whether human genes constitute patent-eligible subject matter under Section 101—is only a "threshold" analysis. *See Bilski v. Kappos*, 561 U.S.___,130 S. Ct. 3218, 3225 (2010) ("The § 101 patent-eligibility inquiry is only a threshold test."); *id.* at 3236 (Stevens, J., concurring in the judgment) ("Section 101 imposes a threshold condition."); *Diehr*, 450 U.S. at 188.

5. This Court has consistently framed the general principles that govern patent-eligible subject matter under 35 U.S.C. § 101 based on two questions:

> 1) Does the claimed subject matter fall within one of the four statutory categories of patent-eligible subject matter: (i) process, (ii) machine, (iii) manufacture, or (iv) composition of matter (or any improvement thereof)?
>
> 2) If so, is the claimed subject matter directed to one of three so-called "fundamental principles," *i.e.*, laws of nature, natural phenomena or abstract ideas, that are exceptions to patent-eligible subject matter?

See Bilski, 130 S. Ct. at 3225; *Diehr*, 450 U.S. at 185 (synthesizing, *inter alia*, *Chakrabarty*, 447 U.S. at 309 (1980); *Parker v. Flook*, 437 U.S. 584, 589 (1978); *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)).

6. In *Mayo*,[4] this Court relied on the notion that if a process claim is broad enough to preempt all uses of a fundamental principle, then the claim must be deemed patent-ineligible. That approach has been criticized in the literature,[5] and the NYIPLA respectfully submits that, as discussed *infra*, the better view should be to reserve the analysis of process claim breadth to the separate patentability analysis under Section 112.

An emerging concept in recent lower court analyses considers whether claim is adequately described and enabled for its "full scope," often referred to as the "commensurateness" principle. *E.g.*, *MagSil Corp. v. Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377, 1380-81 (Fed. Cir. 2011) (Rader, C.J.) ("Enablement serves the dual function in the patent system of ensuring adequate disclosure of the claimed invention and of preventing claims broader than the disclosed invention."); *id.* at 1381 ("The scope of the claims must be less than or equal to the scope of the enablement to ensure that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims.") (quotation and citations omitted).[6]

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[4] *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. ___, 132 S.Ct. 1289, 1294 (2012) (noting that precedent warns "against upholding patents that claim processes that too broadly preempt the use of a natural law") (citations omitted).

[5] Joshua D. Sarnoff, *Patent-Eligible Inventions After* Bilski*: History and Theory*, 63 Hastings Law Journal 53, 91 (2011) ("Concern over 'preempting' applications by patenting claims to applications of science, nature and ideas is both misleading and unhelpful. Preemption is a misleading concept because the scope of a claimed invention simply is *not* the relevant question for eligibility. . . . Preemption is unhelpful because it changes the focus from the nature of the invention for which patent protection is sought, and from the requisite judgments of human creativity or similarity, onto the consequence of granting protection; that is, it puts the cart of the conclusion before the horse of one of its premises.") (internal citations omitted) (emphasis in original).

If Myriad's claims were construed as broadly as Petitioners argue, they might indeed fall within an exception to patent eligibility. But the claims before the Court are directed to isolated DNA molecules: specific, identified chemicals that do not exist in nature. Human intervention is required to convert a full-length naturally-occurring DNA molecule within human cells into the claimed chemical compounds which are patent-eligible under Section 101 as compositions of matter and manufactures.

SUMMARY OF ARGUMENT

The patents in this case are not patents on life. The claims at issue do not patent or preempt any individual's naturally-occurring DNA. Nor can the claims be infringed by a human's mere existence. Rather, the claims are limited to specific chemical compounds that can only be produced by purposeful and directed human activity. Those "pioneer" patents, which occasionally appear, certainly should not be deemed patent-ineligible simply because their disclosures are important and comprehensive.

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[6] So long as a process claim contains sufficient limitations to facilitate the requisite analysis under Section 112 as required by *MagSil*, it should pass muster under Section 101.

The considerable public debate and deeper philosophical analysis that has surrounded the facts of this case are largely irrelevant to this Court's interpretations of the Patent Act. The legal precedents that should govern the analysis under Section 101 broadly confer patent eligibility upon non-naturally-occurring compositions of matter and manufactures such as the DNA molecules claimed by Myriad's patents.

This Court's precedent has established clear rules governing the scope of patent-eligible subject matter—rules that should inform the disposition of this case. Inventions covering compositions of matter and manufactures may be patented provided that the invention does not cover a patent-ineligible fundamental principle. The claims at issue are directed to human-made molecules that are not found in nature. Whether the claims at issue may ultimately suffer from other defects that preclude patentability is an issue not now before the Court. But the inventions recited, as a threshold matter, under *Chakrabarty*, are directed to patent-eligible subject matter.

Moreover, Congress has had ample opportunity to consider whether patents directed to naturally-occurring DNA sequences, like human genes, should continue to enjoy patent protection. So too has Congress had the opportunity to legislatively adjust the judicially created exceptions to patent-eligible subject matter. Yet Congress has consistently declined to adopt the position that Petitioners seek through the judicial imprimatur of this Court.

Based on the points below, NYIPLA respectfully submits that the Court should confirm the patent eligibility of compositions of matter and manufactures created by human intervention. As this Court has recognized, patent eligibility is only a threshold question, and the ultimate conclusion as to an inventor's right to exclude should be reserved for the holistic analysis of all conditions of patentability required by the Patent Act.

In reaching this conclusion, the Court also will endorse and reaffirm the decades-old practice of the PTO respecting the broad scope of patent-eligible subject matter germane to the critical biotechnology, pharmaceutical and health care industries. Those engaged in research and development in those industries, and the financing thereof, expect and deserve a clear statement from this Court that their innovations will continue to benefit from the value created by patent protection.

ARGUMENT

I. Well-settled principles governing patent-eligible subject matter should be applied to the claims at issue.

For more than thirty years, this Court has consistently applied a two-step inquiry as the standard for determining the patent eligibility of an invention under Section 101. The first step is to determine whether the subject matter of the claimed invention falls within one of the four categories of patent-eligible subject matter set forth in 35 U.S.C. § 101: processes, machines, compositions of matter, or manufactures. *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 483 (1974) ("[N]o patent is available for a discovery, however useful, novel, and nonobvious, unless it falls within the express categories of patentable subject matter.").

The second step is to determine whether the claimed subject matter is directed to one of the three so-called "fundamental principles:" "laws of nature, natural phenomena and abstract ideas." *Chakrabarty*, 447 U.S. at 309 (citations omitted); *see Bilski*, 130 S. Ct. at 3225 (2010) (quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)).

This Court has consistently applied this standard since *Chakrabarty*, and reaffirmed it most recently in *Mayo*. 132 S. Ct. at 1293.[7] In fact, the *Mayo* Court rejected "shortcuts" like the Federal Circuit's "machine-or-transformation" test as a suitable proxy for the two-step patent eligibility analysis commanded by precedent. *Id.* at 1303 (confirming that the Court has "neither said nor implied that the ["machine-or-transformation"] test trumps the 'law of nature' exception").

The Association respectfully submits that this standard is a clear and logical application of the Congressional purpose in enacting and codifying the Patent Act. It meets the settled expectations of practitioners, on the one hand, and those of patentees and their industries on the other. It has functioned well for over thirty years, permitting a broad scope for examining patent applications covering useful inventions that have advanced Science and useful Arts at an unprecedented rate. At the same time, the standard safeguards access to information and supports the public's expectation of continued innovation.

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[7] The PTO likewise applies this Court's two-step inquiry as the standard for determining patent-eligible subject matter under 35 U.S.C. § 101. *See* MPEP § 2106.

A. The claimed inventions cover man-made compositions of matter and manufactures, satisfying the first step of the Section 101 analysis.

The isolated DNA molecules of the claims at issue are "compositions of matter," which this Court has defined as a composition of two or more substances or a composite article, whether the result of chemical union or of mechanical mixture, and whether of gas, fluid, powder or solid. *Chakrabarty*, 447 U.S. at 308 (quoting *Shell Development Co. v. Watson*, 149 F. Supp. 279, 280 (D.D.C. 1957), *aff'd*, 252 F.2d 861 (D.C. Cir. 1958) (per curiam)); *see P.E. Sharpless Co. v. Crawford Farms, Inc.*, 287 F. 655, 658 (2d Cir. 1923) (further stating that there is "no restriction as to the nature of the composition which may be patented"); *see also* Pet. App. 48a (noting that the "parties and the government appear to agree that isolated DNAs are compositions of matter, they disagree on whether and to what degree such molecules fall within the exception for products of nature").

The isolated DNA molecules of the claims at issue are also "manufactures," which this Court has defined, consistent with its dictionary definition, as "the production of articles for use from raw or prepared materials by giving to these materials new forms, qualities, properties, or combinations, whether by hand-labor or machinery." *Chakrabarty*, 447 U.S. at 308 (quoting *Am. Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1, 11 (1931)).

The claimed subject matter thus satisfies the first step of the Section 101 analysis by fitting into at least one of the statutory categories.

B. No judicial exception to patent eligibility applies to the claims at issue.

Claimed subject matter that falls within at least one of the four statutory categories, may not be patent-eligible if it is directed to a law of nature, a natural phenomena or an abstract idea—the only judicially-created exceptions to patent eligibility. *Chakrabarty*, 447 U.S. at 309. With regard to products of nature, however, *Chakrabarty* confirms that new products having "markedly different characteristics from [those] found in nature" are patent-eligible discoveries that are "not nature's handiwork," but that of the inventor—in other words, human-made and patent-eligible. *Id.* at 310.

1. DNA molecules made through human intervention cannot be products of nature.

In this case, the lower courts disagreed as to which characteristics of isolated DNA are relevant to determine patent eligibility. The district court focused on the DNA *sequence* to reach its conclusion that the claimed isolated DNA molecules did not represent "a change that results in the creation of a fundamentally new product." Pet. App. 320a-21a, 336a, 344a.

The court of appeals, however, focused on the DNA chemical structure to reach its conclusion that the claimed isolated DNA molecules were "markedly different" from their naturally-occurring counterparts, and patent-eligible composition that have "distinctive characteristics" resulting from human intervention. Pet. App. 50a-53a.

The dual nature of isolated DNA as *both* a carrier of genetic information (sequence) and a specific chemical compound (nucleotides) conflates these two positions—two sides of the same coin that support the conclusion that an isolated DNA molecule is patent-eligible under 35 U.S.C. § 101. Accordingly, however viewed, the Association respectfully submits that creating a useful, isolated DNA molecule is undeniably a product of human intervention—and therefore meets the standard for patent eligibility.

Isolation is a rational step that requires an informed decision of what nucleotide structural units (bases) to include in the molecule when cleaving it from its natural environment. Isolation is a significant and consequential step reflecting the handiwork of man, and thus creating a composition of matter, and a manufacture, that is neither a law nor a product of nature, and is therefore patent-eligible.

In light of the complex *in vivo* structure and function of a gene as it exists naturally in a unified chromosome, isolation of that gene—or a defined subpart of it—is an activity that falls on the patent-eligible side of the clear dividing line between patent-ineligible "natural phenomena" and patent-eligible "human-made inventions." *J.E.M.*, 534 U.S. at 130. *See Chakrabarty*, *supra*. This is especially so when the end result of isolation is the production of a distinct chemical compound that does not exist in nature and cannot be a "natural product," as in this case, as twice recognized by the court of appeals below.

Further, this Court has recognized that Congress specifically intended that patentable subject matter "include anything under the sun *that is made by man*." *Chakrabarty*, 447 U.S. at 309 (emphasis added) (quoting S. Rep. No. 82-1979, at 5 (1952); H.R. Rep. No. 82-1923, at 6 (1952)). For the same reason, human activity generating "newly developed plant breeds" falls within the ambit of Section 101, even though other statutes provide protection for plants. *J.E.M.*, 534 U.S. at 144 (identifying Section 101 and the Plant Variety Protection Act ("PVPA") as overlapping statutes that have effect because "many plant varieties that are unable to satisfy the stringent requirements of § 101 might still qualify for the lesser protections afforded by the PVPA").

Taken as a whole, this Court's precedent firmly establishes a product of human intervention as critical to expressly removing living subject matter from the category of patent-ineligible "natural phenomenon."

2. Isolated DNA is not a discovery of the handiwork of nature.

In *Mayo*, this Court asked whether an "inventive concept" existed in a process claim that "add[ed] enough" to a law of nature or natural phenomenon "sufficient to ensure that the patent in practice amounts to significantly more than a patent on the natural law itself." 132 S.Ct. at 1294, 1300. For a claimed process or method, this "inventive concept" is an analysis that delineates specific *human activity* as separate and apart from *natural activity* that standing alone is not patent-eligible.

By suggesting that human effort alone, without more, is insufficient to convert an invention from patent-ineligible to patent-eligible, Petitioners invite this Court to extend the "inventive concept" applicable to processes and methods to analyze the patent eligibility of compositions of matter and manufactures. *See* Pet. Br. at 36-37. The Association respectfully submits that the Court should decline this invitation.

When human intervention produces an isolated DNA molecule, it becomes a unique chemical that represents *direct evidence* of the human activity that the Court found lacking in the patent claims at issue in *Mayo*. 132 S. Ct. at 1302 (concluding that the additional steps in the claimed method "add nothing of significance to the natural laws themselves"). Isolated DNA molecules are not genes, human or otherwise, but are the end result of the applied human activity necessary to confer patent eligibility; thus, it would be redundant to turn to an "inventive concept" as a proxy for the human activity plainly present. In short, isolated DNA molecules are not nature's handiwork. *See Chakrabarty*, 447 U.S. at 310.

For this reason, Petitioners' reliance on *Funk Brothers*[8] is misplaced. *See* Pet. Br. at 37-38. There, the invention concerned the simple mixture of different strains of bacteria to create a composition of matter retaining the natural properties of each strain. In contrast, isolated DNA *does not* retain all of the naturally-occurring properties of its source. Removed from its native environment in the gene of the chromosome, isolated DNA is not subject to the complex genetic regulatory processes that confer full functionality of a gene *in vivo*. An isolated DNA molecule may possess some but never all of the naturally-occurring properties of a gene *in vivo*. Isolated DNA is always "markedly different" from the gene from which it was extracted. *Chakrabarty*, 447 U.S. at 310.

Like the pre-1952 claimed invention in *Funk Brothers*, the isolated DNA molecules of Myriad's claims fall squarely within the statutory definition for an "invention" as codified in 1952. In 35 U.S.C. § 100(a), the Patent

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[8] *Funk Bros. Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948).

Act expressly defines an "invention" as "invention and discovery." 35 U.S.C. § 100(a). This definition was retained in the 1952 Amendments. In fact, the originally proposed amendments contained the following description:

> Discoveries, as well as inventions, may be patented, *if the discovery can be expressed in terms of or embodied in a new and useful* art, machine, *manufacture or composition of matter*, or improvement thereof, and the term invention when used in this title includes such discovery.

H. Comm. on the Judiciary, 81st Cong., Proposed Revision and Amendment of the Patent Laws 11 (Comm. Print. 1950) (emphasis added). Converting a portion of a naturally-occurring gene into a distinct chemical entity—an isolated DNA molecule—is the conversion of a portion of a naturally-occurring gene into a useful composition of matter or manufacture through human intervention. This creates an invention within the scope of Section 101. The source material, which is not claimed, remains a fundamental principle ineligible for patenting.

Claims directed to isolated DNA molecules having a particular structure (*i.e.*, a specific sequence of nucleotide bases) or function (*e.g.*, capacity to encode and express a protein) necessarily evoke non-naturally-occurring subject matter. Under this Court's precedent, such claims are not directed to a patent-ineligible "fundamental principle," but are patent-eligible under Section 101.

3. Isolated DNA molecules, though patent-eligible under Section 101, may not meet the other conditions of patentability under Sections 102, 103 or 112.

Determining whether a patent-eligible claim is actually patentable—that is, satisfies the "conditions and requirements" of Title 35—necessitates an analysis separate from the patent eligibility inquiry. 35 U.S.C. § 101. *See Bilski, supra.*

Given the narrow ambit of the question presented to this Court on certiorari, and the fact that neither the district court nor the court of appeals has yet considered whether the isolated DNA claims at issue meet the other statutory conditions and requirements for patentability, it seems highly unlikely that this Court would wish to address patentability in this proceeding. Nevertheless, and despite the fact that Section 101 generally deals only with the threshold question of whether a claimed invention is patent-eligible, a few brief comments on three statutory criteria for patentability may be in order.

a. Sections 102 and 103

This Court's clear proscription in *Bilski* against conflating the patent eligibility and patentability inquiries is particularly important where rapid technological advances affecting the novelty and obviousness analyses can tempt the district courts to apply the prohibited technique. As this Court stated in *Diehr*,

> The "novelty" of any element or steps in a process, or even of the process itself, is of no

> relevance in determining whether the subject matter of a claim falls within the § 101 categories of possibly patentable subject matter.

450 U.S. at 188-89. *See id.* at 193 n.15 (concluding that "the fact that one or more of the steps in respondents' process may not, in isolation, be novel or independently eligible for patent protection is irrelevant to the question of whether the claims as a whole recite subject matter *eligible* for patent protection under § 101") (emphasis in original).

In this case, moreover, neither the district court nor the court of appeals has yet considered the question of whether the isolated DNA claims at issue failed to meet the conditions for patentability set forth in Sections 102 and 103.

The NYIPLA recognizes that in the three decades since *Chakrabarty* the levels of ordinary skill in the arts of biotechnology and the isolation and modification of genetic material have increased dramatically. Indeed, advances in laboratory technologies have enabled procedures once considered worthy of the Nobel Prize to be assigned to non-degreed workers in contemporary laboratories. The improved processes for carrying out the polymerase chain reaction ("PCR") represent one example.[9] Courts and commentators alike also have noted that (a) near completion of the massive efforts to sequence the human genome and (b) widespread university and private corporate efforts to assign potential functionalities to certain isolated DNA molecules corresponding to genes could render claims directed to those functionalities obvious under Section 103. *See, e.g.*, *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (holding a claim directed to a gene obvious where "the prior art [taught] the protein of interest, a motivation to isolate the gene coding for that protein, and illustrative instructions . . . for cloning this gene"); Christopher M. Holman, *Trends in Human Gene Patent Litigation*, 322 SCIENCE 198, 199 (2008) (noting the steep decline in human gene patents and applications following the human genome's publication in 2001).

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[9] Kary B. Mullis shared the 1993 Nobel Prize in Chemistry for his development of an improvement to the polymerase chain reaction ("PCR") made at Cetus Corporation ("Cetus") in 1983. Kary B. Mullis, Nobel Lecture: The Polymerase Chain Reaction (Dec. 8, 1993) (available at http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1993/mullis-lecture.html) (last accessed Mar. 13, 2013). As might be expected, a number of patents were issued to Cetus on various aspects of this development. *See*

Nevertheless, in this case as in *Funk Brothers*, the lower courts did not hear facts relating to novelty or obviousness at all, limiting the factual record below and restricting the court of appeals analysis to patent eligibility under Section 101.

Brief Of New York Intellectual Property Law Association As *Amicus Curiae* In Support of Petitioner at 22 n.31, *Merck KGaA v. Integra Lifesciences, Ltd.*, 545 U.S. 193 (2005) (No. 03-1237), 2005 WL 460873. *See also* the discussion of *Taq* polymerase in Susan McBee and Bryan Jones, The Supreme Court should be mindful of naturally derived products other than nucleic acids when deciding Myriad, SCOTUSblog (Feb. 7, 2013, 10:16 AM), http://www.scotusblog.com/2013/02/ the-supreme-court-should-be-mindful-of-naturally-derived-products-other-than-nucleic-acids-when-deciding-myriad/.

b. Section 112

Likewise, Petitioner's argument repeatedly refers to the breadth of the claims at-issue, characterized as extending "to the genes themselves and reach all structures and uses of the gene" that would include both known and unknown variations. *See* Pet. Br. at 3, 11-16. But breadth necessarily implicates an issue sometimes referred to as "commensurateness": whether a claim is adequately described or enabled throughout its "full scope." *See* 35 U.S.C. § 112(a) ("The specification shall contain . . . the manner and process of making and using [the invention]."). *See also Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1353-54 (Fed. Cir. 2010) (en banc) (stating that the written description requirement ensures that "the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification") (quotation and citations omitted); *MagSil, supra*. This too the courts below neither considered nor determined.

The NYIPLA respectfully submits that the "patentability" of the claims at issue can only be resolved, and the patentability of the isolated DNA from a human gene, can only be established by considering *all* potential grounds for invalidity. This holistic approach allows each of the conditions for patentability to properly limit the claimed inventions to those that Congress intended should enjoy protection. It would be both improper and impractical to graft aspects of substantive patentability analyses onto the threshold consideration of patent eligibility under Section 101. *See Bilski*, 130 S.Ct. at 3225.

II. Congressional action and intent has repeatedly implied broad support for biotechnology, including patent eligibility for inventions involving human genes.

Congress has already set clear policy concerning biotechnology patents, including patents involving human genes. Such inventions should remain patent-eligible under Section 101 unless and until Congress indicates otherwise. Congress is fully capable of making statutory amendments that specifically exempt past and future activities from patent eligibility. *E.g.*, 42 U.S.C. § 2181(a) ("No patent shall hereafter be granted for any invention or discovery which is useful solely in the utilization of special nuclear material or atomic energy in an atomic weapon."). By creating an exception for one category of subject matter, while failing to carve out "gene patents" in the same manner, Congress impliedly chose not to disturb the patent eligibility of isolated DNA molecules obtained by human intervention upon human genomic DNA—an activity the PTO has permitted for more than thirty years.

A. The Court has confirmed Congress' broad grant of subject matter eligibility.

The future direction of human innovation is impossible to predict. This limitation requires that the patent laws remain a "dynamic provision designed to encompass new and unforeseen inventions." *J.E.M.*, 534 U.S. at 135. Broad subject matter eligibility should remain a cornerstone of this dynamic approach to patentable inventions.

This Court recently concluded that a "categorical rule denying patent protection for 'inventions in areas not contemplated by Congress . . . would frustrate the purposes of the patent law.'" *Bilski*, 130 S.Ct. at 3227 (quoting *Chakrabarty*, 47 U.S. at 315). The *Chakrabarty* Court confirmed this expansive view when it cited the Committee Reports accompanying the 1952 Patent Act as evidence of the intent of Congress to achieve broad subject matter eligibility consistent with Thomas Jefferson's "liberal encouragement" of ingenuity. 447 U.S. at 308-09 (quoting 5 Writings of Thomas Jefferson 75-76 (Washington ed.) 1871). More than a century before *Chakrabarty*, this Court had expressed the same general principle:

> The true policy and ends of the patent laws enacted under this Government are disclosed in that article of the Constitution, the source of all these laws, *viz*: 'to promote the progress of science and the useful arts,' contemplating and necessarily implying their extension, and increasing adaptation to the uses of society.

Kendall v. Winsor, 62 U.S. (21 How.) 322, 328 (1859).

Absent a clear statement from Congress to the contrary, the NYIPLA respectfully submits that this Court should continue to respect the broad patent eligibility for "anything under the sun that is made by man," which, as discussed above, would include the isolated DNA molecules claimed by Myriad.

B. Congress' acts and omissions suggest its continued support for patent eligibility for gene patents.

Beyond its holding that human-made compositions of matter and manufactures (versus products of nature) should be eligible for patent protection, *Chakrabarty* is a fitting cornerstone for this Court's analysis because its holding and the modern molecular biology revolution have matured in tandem. In the three decades since *Chakrabarty*, Congress has not taken any action that would limit the broad applicability of the Patent Act to reach biotechnology applications in general, and modified genetic material in particular. The NYIPLA respectfully submits that this case is not an appropriate vehicle for the Court to substitute its judgment for that of Congress'.

1. In 1995, Congress amended the Patent Act to address conditions of patentability related to "biotechnological process" patents. *See* Pub. L. No. 104-41, 109 Stat. 351-52 (Nov. 1, 1995). Congress defined "biotechnological process" broadly to cover fused cells and genetically altered organisms that express either: (*i*) an exogenous nucleotide sequence, (*ii*) an endogenous nucleotide sequence in a different manner than in that organism in nature, or (iii) non-naturally-occurring physiological characteristics, and methods of using the products produced by such processes. 35 U.S.C. § 103(b)(3). *See also* Biotechnology Patent Protection Act of 1991, S.654, 102nd Cong. (1991) (proposing amendment to 35 U.S.C. § 103 to reach a "biotechnological process," defined as "any method of making *or using* living organisms . . . for the purpose of *making or modifying products*") (emphasis added).

Importantly, the exogenous and endogenous nucleotide sequences referenced in Congress' definition do not exclude isolated DNA, let alone human genes, suggesting Congress' understanding at the time that patents, which the PTO had then been issuing for over a dozen years, should continue to issue covering isolated DNA and its use in biotechnological processes. It stands to reason that subject matter defined in the Patent Act necessarily should qualify as patent-eligible subject matter under Section 101.

2. In 1996, Congress amended the Patent Act again to limit medical practitioners' liability for patent infringement, specifically exempting infringement liability for "the practice of a process in violation of a biotechnology patent." 35 U.S.C. § 287(c)(2)(A)(iii); *see* 110 Stat. 3009-67. Congress specifically identified biotechnology patents as those making use of, *inter alia*, "genetic materials, such as DNA and RNA that is obtained from within the cell." 142 Cong. Rec. H11866 (daily ed. Sep. 28, 1996). Indeed, Senator Hatch specifically recognized that, under *Chakrabarty* and *Diehr*, Section 101 should be interpreted broadly to "encompass unforeseeable future developments." 142 Cong. Rec. S11844 (daily ed. Sep. 30, 1996). Therefore, Congress enacted Section 287(c) specifically knowing that future biotechnology patents might issue in a medical, *i.e.*, human, context, and specifically sought to shield medical practitioners from liability for infringement. This is a clear indication that Congress did not disapprove of biotechnology patents covering DNA and RNA obtained from naturally-occurring cells, like human cells, and that uses of such isolated DNA might infringe a patent in a medical context. Congress' acquiescence in this instance demonstrates its

understanding that the scope of patent-eligible subject matter under Section 101 is broad enough to reach isolated DNA molecules, including those corresponding to human genes in whole or in part.

3. In 2007, Representatives Becerra (D-CA) and Weldon (R-FL) introduced the Genomic Research and Accessibility Act that proposed amending the Patent Act to prohibit patenting "human genetic material," providing:

> Notwithstanding any other provision of law, no patent may be obtained for a nucleotide sequence, or its functions or correlations, or the naturally occurring products it specifies.

H.R. 977, 110th Cong. § 2(a) (2007). In introducing the bill, Rep. Becerra's extended remarks noted that the "practice of gene patenting, where private corporations, universities and even the Federal Government are granted a monopoly by the United States Patent and Trademark Office on significant sections of the human genome" has "dramatic, costly and harmful implications for every American." 153 Cong Rec. E316 (Feb. 9, 2007). Quoting *Chakrabarty*, the remarks identified the true nature of the problem to be addressed:

> Proponents of gene patenting have said they are not patenting genes but instead are patenting "isolated and purified" genetic sequences. This is mere wordplay. In practice, these patents are patents on products of nature.

Id.

After referring the bill to the House Judiciary Committee, and then to the House Subcommittee on Courts, the Internet, and Intellectual Property, Congress took no further action on the proposed legislation that would accomplish the very same outcome Petitioners seek from this Court. The Association respectfully submits that the courts should refrain from adopting policy positions that Congress specifically considered but declined to pursue.

4. In 2011, Congress passed the America Invents Act, which expressly excluded a "human organism" from patent eligibility. Pub. L. 112-29, Sep. 16, 2011 (H.R. 1249) § 33(a). This provision was consistent with the PTO's interpretation of Section 101 that a claim encompassing a human being is not patent-eligible. 1077 Off. Gaz. Pat. Office 24 (April 21, 1987); *see also* MPEP § 2105 (explaining that a patent claim should be rejected under 35 U.S.C. § 101 if, under its "broadest interpretation," the "claimed invention as a whole encompasses a human being"). Rep. Weldon, the sponsor, confirmed that this exclusion did not extend to gene patents. 157 Cong. Rec. E1178 (daily ed. Jun. 23, 2011) (speech of Rep. Weldon) ("I would like to add, Mr. Chairman, that this has no bearing on stem cell research or patenting genes, it only affects patenting human organisms, human embryos, human fetuses or human beings.").

Congress' intent is clear that "[c]onsistent with the current law, the genetic inventions that form the basis for . . . diagnostic tests *are eligible for patenting. . . .*" 157 Cong. Rec. E1183 (daily ed. Jun. 22, 2011) (remarks of Rep. L. Smith) (emphasis supplied). Notably, Rep. Weldon's human organism exception to patent eligibility had been pending for years in Congress when the district court's decision below issued in 2009 invalidating the patents-in-suit.

Moreover in considering the Weldon Amendment, Congress' intent was clear that

> nothing in this section should be construed to limit the ability of the PTO to issue a patent containing claims directed to or encompassing:
>
> 1. *any chemical compound or composition*, whether obtained from animals or human beings or produced synthetically, and *whether identical to or distinct from a chemical structure as found in an animal or human being*, including but not limited to *nucleic acids*, polypeptides, proteins, antibodies and hormones. . . .

Id. (emphasis added). Congress therefore appreciated that it could have restricted patenting for isolated DNA molecules corresponding to human genes such as those claimed in this case, yet specifically chose to permit such patents to preserve "economic viability of the biotechnology industry." *Id.*[10]

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[10] This legislation also provides for a PTO study on genetic diagnostic testing, and a report thereafter to Congress. According to the statute,

> [t]he Director shall conduct a study on effective ways to provide independent, confirming genetic diagnostic test activity where gene patents and exclusive licensing for primary genetic diagnostic tests exist.

Pub. L. 112-29, Sep. 16, 2011 (H.R. 1249) § 27. Congress is already addressing the considerable public debate and deeper philosophical questions surrounding the facts of this case.

It is clear that Congress has long been in an ideal position to consider whether patents directed to isolated DNA molecules derived from a human gene should no longer enjoy patent protection. Congress' decisions not to act over the years, in the face of proposed legislation essentially raising the Question Presented, should be respected, suggesting that it might be improper for this Court to judicially create an exclusion under Section 101 where no intent exists from Congress to do so.

CONCLUSION

For the foregoing reasons, the decision of the court of appeals should be affirmed.

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March 14, 2013

AMICUS
CURIAE
BRIEF

AN
BRIEFS

SUPREME COURT, U.S.
FILED
MAR 14 2013
OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,
Petitioners,

v.

MYRIAD GENETICS, INC., ET AL.,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

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INTEREST OF AMICUS CURIAE

The Pharmaceutical Research and Manufacturers of America (PhRMA) is a voluntary, nonprofit association representing the nation's leading research-based pharmaceutical and biotechnology companies, which are the primary source of the many new drugs and biologics introduced each year.[1] *See* PHRMA MEMBER COMPANIES, *at* http://www.phrma.org/about/member-companies (last visited March 13, 2013).

There is significant diagnostic, therapeutic, and commercial value in isolated and purified biological materials. Innovators such as PhRMA's members are at the forefront of the breakthroughs involving these materials. In 2011 alone, PhRMA members invested nearly $50 billion in researching and developing new medications and vaccines that help patients live longer, healthier and more productive lives. *See* 2012 PHARM. INDUS. PROFILE, *at* http://www.phrma.org/sites/default/files/159/phrma_industry_profile.pdf (last visited March 13, 2013).

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[1] Pursuant to this Court's Rule 37.6, *amicus* affirms that no counsel for any party authored this brief in whole or in part, that no party or counsel for a party made a monetary contribution intended to fund the preparation or submission of this brief, and that no person other than amicus or its counsel made a monetary contribution intended to fund the preparation or submission of this brief. The parties have consented in writing to the filing of this brief.

In light of the great uncertainties and risks inherent in the development of medicines, PhRMA's members depend on a degree of certainty and predictability in patent law. For decades, PhRMA's members have invested in biotech research and development based on an assurance of the availability of patent exclusivity. In making investment decisions, PhRMA's members have relied upon a statutory framework that provides broad patent eligibility, decades of jurisprudence granting patent protection to isolated and purified biological materials (including isolated DNA molecules), and the USPTO's longstanding policy and practice. Accordingly, PhRMA urges the Court to uphold the settled expectations of innovators and clarify that although genes as they exist in the human body are not patent-eligible, "isolated" genes result from human intervention and ingenuity and thus are patent-eligible.

SUMMARY OF ARGUMENT

1. Human genes as they exist in the body are not patentable. But the patents at issue do not claim human genes as they exist in the body. Instead, the patents at issue claim isolated DNA molecules. This is a critical distinction. Although "native" genes and "isolated" DNA molecules both contain informational content capable of encoding a BRCA1/BRCA2 polypeptide, the similarities end there. Native genes exist as an unknown part of a complex host organism genome, embedded in much larger genomic sequences and surrounded by other cellular components. Extensive human intervention is

required to isolate specific DNA molecules from this complex matrix. Each claimed isolated DNA molecule is a tangible, human-made chemical compound that differs in structure, function, utility, and informational content from its native counterpart. Therefore, none of the patent claims at issue in this case read on genes as they exist in the human body.

2. Patent owners making research and development investment decisions have long relied on a statutory framework that provides broad patent eligibility, decades of jurisprudence recognizing isolated and purified biological materials as patent-eligible subject matter, and the USPTO's longstanding policy and practice with respect to those inventions. These settled expectations and substantial property rights should not be ignored. The discovery and development of new drug therapies and diagnostic tools is crucial to public health. The protections afforded by the federal patent laws are central to providing appropriate incentives to overcome the staggering costs and risks of developing new products and therapies.

3. Patent protection provides innovators with a limited period of exclusivity in order to encourage them to incur these enormous up-front costs and risks. In the pharmaceutical field in particular, because patent filings must be made years in advance of regulatory approval, research and development investment decisions necessarily depend on a degree of certainty and predictability in patent law—including certainty that the fruits of such research endeavors are patent-eligible.

The strength of the U.S. patent system depends upon the carefully calibrated balance of protecting and rewarding ingenuity in exchange for public disclosure. It is essential to provide appropriate incentives for continued innovation, particularly in the field of biotechnology. Over the past several decades, Congress has witnessed the USPTO grant thousands of patents claiming isolated DNA sequences and has opted to maintain the patent eligibility of these inventions. Because Congress is responsible for enacting legislation to "promote the progress of science and useful arts," the Petitioner's policy-driven arguments should be addressed to Congress, not to this Court.

ARGUMENT

I. Native Genes and Isolated DNA Molecules Are Fundamentally Different.

A. Native Genes Exist as Part of a Complex Host Organism Genome.

Living organisms contain genes composed of deoxyribonucleic acid (DNA). BRUCE ALBERTS ET AL., MOLECULAR BIOLOGY OF THE CELL 191 (4th ed. 2002) ("*Molecular Biology*"). These genes encode inherited genetic information and play a critical role in organism function. *Id.* More specifically, genes specify, or encode, peptide chains of amino acids that form proteins, which are the building blocks of living organisms and perform a vast array of functions, including catalyzing metabolic reactions, responding to stimuli, and even regulating the expression of other genes. *Id.* at 198. Native genes exist as an unknown part of a complex host organism genome, embedded in much larger genomic sequences and surrounded by other cellular components. *Id.* at 207. Genes fulfilling particular functions are often given specific names, such as BRCA1/BRCA2 genes.

The human genome is composed of DNA. DNA as it exists in the human body (genomic DNA) is packaged into chromatin, which, in turn, forms chromosomes—long strands of DNA that contain many genes—and are associated with various proteins called histones. *Id.* Histones and other chromatin proteins define the conformation of the chromatin—information arguably as important in gene expression as the underlying DNA sequence itself. *Id.* at 207-08. A human being has twenty-three chromosome pairs, a full copy of which is contained in most human cells. *Id.* at 198.

The basic building blocks of DNA are repeating units of four nucleotide bases (adenine (A), thymine (T), cytosine (C), and guanine (G)), linked together via a phosphate sugar backbone. *Id.* at 193. In living organisms, DNA consists of two paired, but separate, DNA strands that form a double helix. *Id.* at 193-94. Generally, one of the strands is a "coding strand," and the other is a complementary "template" strand. *Id.* at 195-96. For example, the A on one strand pairs with the T of the complementary strand, the C on one strand pairs with the G of the complementary strand; and vice versa. The specific order of nucleotide bases that form a DNA strand is often referred to as a DNA sequence or gene sequence. *Id.* at 196.

Native DNA sequences contain both coding regions ("exons") and non-coding regions ("introns").

Id. at 202. These exons and introns are important to the creation of a protein from a DNA sequence. *Id.* at 317. In native DNA, introns represent the vast majority of a DNA sequence. *Id.*

At a basic level, protein creation results from two iterative processes, called transcription and translation. *Id.* at 302. Transcription is the process by which the information in the DNA sequence is transferred to a ribonucleic acid sequence. *Id.* Ribonucleic acid or RNA, is another nucleic acid in the body. *Id.* Similar in many respects to DNA, RNA is composed of four nucleotide building blocks, three of which (A, C, and G) are the same as DNA. *Id.* RNA however uses uracil (U) instead of the T in DNA. *Id.* These nucleotide building blocks are held together by a sugar phosphate backbone similar to the one used in DNA. *Id.*

When transcription begins, the DNA double helix is unwound, and the template DNA strand forms the template for the creation of a complementary RNA strand. *Id.* at 303. This RNA strand has the same sequence as the coding DNA strand, except that any Ts in the DNA sequence of the coding DNA strand are replaced by Us in the RNA sequence. Once this RNA sequence is created, the intron coding sections are removed, and the remaining exon sections are spliced together to create "messenger RNA" or mRNA. *Id.* at 317. Figure 1, below, demonstrates this process.

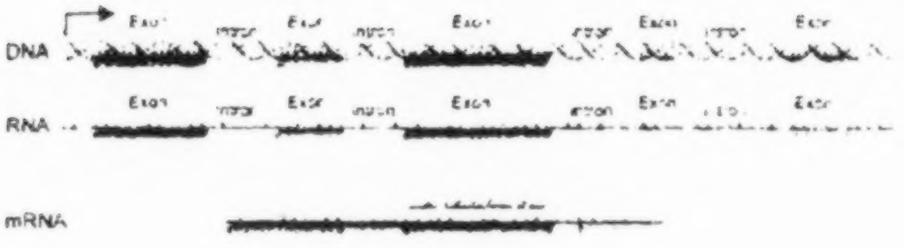

Figure 1

National Human Genome Research Institute *available* at http://www.genome.gov/Images/EdKit/bio2i_large.gif (last accessed March 13, 2013).

Translation occurs when the mRNA is used to create a particular protein. *Molecular Biology*, at 336. Proteins are made up of amino acids, which correspond to particular three-nucleotide combinations found in the mRNA. *Id.* These combinations are called codons. For example, the three-nucleotide combination CGU codes for the amino acid arginine. *Id.* There are sixty-four possible codons, which code for the twenty natural amino acids; certain codons also signal where the protein should start and stop. *Id.* Figure 2 below demonstrates how a particular mRNA strand (top) is translated into a particular peptide, comprised of specific amino acids (bottom).

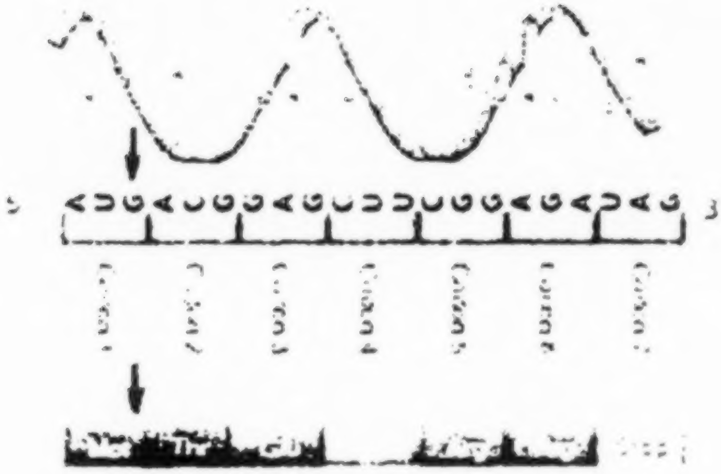

Figure 2

Professor Elizabeth Greyhack Lab, University of Rochester, *available at* http://www.urmc.rochester.edu/labs/Grayhack-Lab/images/geneticcode.png (last accessed March 13, 2013).

Mutations in the native DNA sequence can be extremely problematic. For example, a single nucleotide mutation can lead to the mis-coding of a single amino acid in a particular peptide. Even more serious mutations involve whole portions of a DNA sequence being deleted, rearranged or duplicated, which, in turn, leads to the potential loss or misplacement of particular genes and, accordingly, the proteins for which those genes code. *Molecular Biology*, at 454. Some of these mutations cause a particular disease, or lead to an increased risk of disease.

B. Isolated DNA Molecules and Native DNA Differ in Structure, Function, Utility, and Informational Content.

1. The Claimed BRCA1/BRCA2 Genes Are Distinct From the Section of Native DNA That Encodes the Same Proteins.

DNA as it exists in the human body and isolated DNA molecules differ in significant ways. For example, an isolated DNA sequence can be synthesized from the nucleotide building blocks in a lab. One of the most common forms of this type of isolated DNA molecule is complementary DNA, or cDNA. cDNA is made from a corresponding mRNA template, and therefore lacks many of the intron sequences found in a native gene sequence. For example, some of the claimed BRCA1/BRCA2 sequences, which are cDNA, omit certain non-coding introns (which in some genes account for more than 90 percent of the native gene's length). *See, e.g.*, U.S. Patent No. 5,747,282 (the "'282 patent"), cl. 2 (to 5.9 kb cDNA sequence, which is 1/10th the length of the native BRCA1).

Moreover, a native gene sequence may code for more than one protein. For instance, the longer native BRCA1/BRCA2 genes may be subject to alternative splicing, and thus may code for multiple proteins. *See* Miao Lixia et al., *Alternative Splicing of Breast Cancer Associated Gene BRCA1 from Cancer Cell Line*, J. BIOCHEM. AND MOLECULAR BIO. 15-21 (2007); Ivan Bieche et al., *Increased Level of Exon 12 Alternatively Spliced BRCA2 Transcripts in Tumor Breast Tissue Compared with Normal Tissue*,

J. CANCER RES. 2546-2550 (1999). In contrast, each of the claimed BRCA1 and BRCA2 sequences encode a single protein; again, rendering them distinct from their native counterparts.

2. The Process of Creating Isolated DNA Molecules is Complex and Results in a Chemically Distinct Molecule Relative to their Native Counterparts.

The isolation of DNA is a complex endeavor because DNA is not divided neatly into individual genes. As discussed above, native DNA exists in chromosomes, which are composed of chromatin surrounded by histones. Figure 3, below shows genomic DNA broken down into its component parts. Unlike gold that has been isolated from a stream or a leaf that has been snapped from a tree, these histones are part of, and integral to, the chromatin structure, and therefore, the DNA structure. The removal of this cellular material functionally and structurally alters genomic DNA.

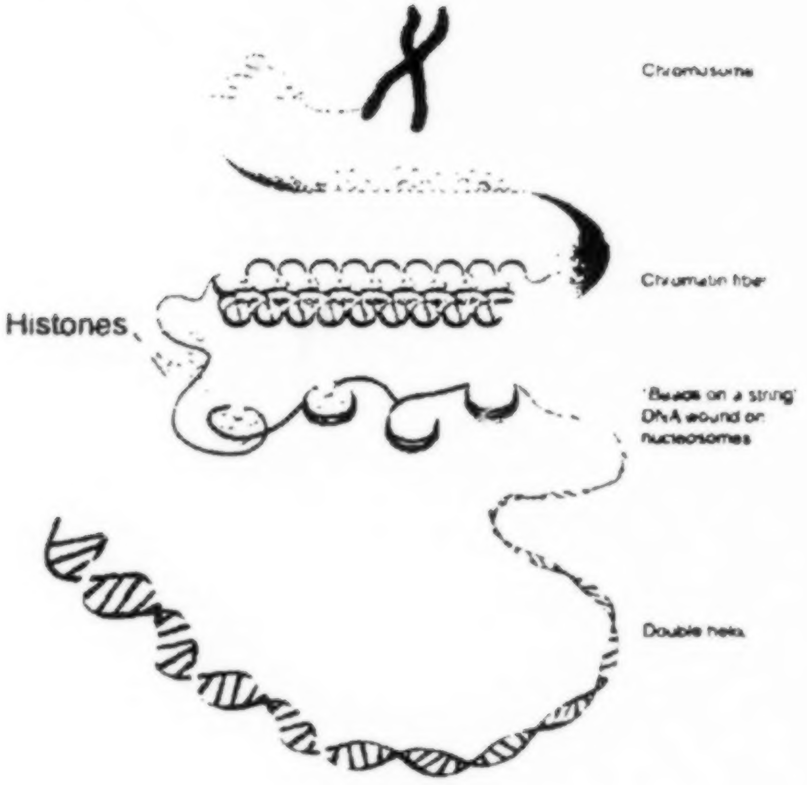
Chromosome
Chromatin fiber
Histones
'Beads on a string' DNA wound on nucleosomes
Double helix

Figure 3

National Human Genome Research Institute *available at* http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85183 (last accessed March 13, 2013).

When genomic DNA is extracted from a living cell, the DNA strand contains multiple genes that are attached to one another, end to end. Locating and excising a particular gene sequence from this genomic DNA is an iterative, complex process that requires specialized knowledge of the gene's composition. After being excised from the genomic DNA, isolated genes are no longer attached to other genes. These isolated genes, like the claimed isolated BRCA1/BRCA2 gene sequences, have free ends. Those free ends do not exist in nature, but are necessary for biotech applications such as end labeling and primer extension, which are important tools in genetic engineering. *Molecular Biology*, at 207, 215–16, 222, 495, 508–09.

Explained another way, isolating a particular DNA molecule is a method of manufacturing that requires two forms of human intervention. First, when extracting the DNA, human intervention is required to physically destroy the cell by rupturing the cell membrane. Second, purifying the extracted DNA molecule requires human intervention to not only remove the material associated with the genomic DNA, but also to excise the particular isolated DNA molecule sought. *See, e.g.*, *Cancer Voices Australia v Myriad Genetics Inc.* [2013] FCA 65, ¶108 (Austr.). These steps result in what is in effect a type of manufactured product.

When isolated, DNA molecules are cleaved from their surrounding cellular material and in the process, they are chemically and functionally altered. This is because the isolated DNA molecule contains the information necessary, but not sufficient, for protein creation. In other words, the process of isolating a DNA molecule results in a distinct chemical entity with distinct attributes as compared to its native counterpart. Contrary to the Petitioner's suggestion, an isolated DNA sequence cannot simply be reinserted into the cell and function as it did previously.

In sum, the claimed isolated DNA sequences do not exist in nature; they are created in a laboratory. Because the claimed isolated DNA sequences are a product of human ingenuity, they are patent-eligible. *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

II. Myriad's Patents Are Directed to Patent-Eligible Subject Matter.

A. Human Genes Differ from the Claimed Isolated DNA Molecules, and Are Not Patentable.

Human genes, as they exist in the human body, are not patent eligible. But the patents at issue in this case do not claim human genes as they exist in the human body. Rather, certain patent claims at issue are directed to "isolated" DNA molecules encoding BRCA1/BRCA2 polypeptides and related diagnostic and therapeutic methods. As defined by the patentee, the invention is limited to DNA that "has been removed from its naturally occurring environment." *See* '282 patent, col. 19, lines 8-19.

The claimed isolated DNA molecules differ in "name, characteristics, and use" from their native counterparts and, as such, constitute patent-eligible subject matter. *Chakrabarty*, 447 U.S. at 309-310 (holding that the claimed invention was "a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity 'having a distinctive name, character [and] use'").[2]

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[2] Although this brief will focus on the issue of patent eligibility, PhRMA agrees with the Respondents that the Petitioners lack standing.

B. Isolated DNA Sequences Fall Within the Broad Realm of Patent-Eligible Subject Matter.

Section 101 defines the subject matter that may be patented under the Patent Act as "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof . . . subject to the conditions and requirements of this title." 35 U.S.C. § 101. Congress adopted this expansive definition by design, recognizing that "ingenuity should receive a liberal encouragement." *Chakrabarty*, 447 U.S. at 308-309 (quoting 5 Writings of Thomas Jefferson 75-76 (H. Washington ed. 1871)). Only the laws of nature, physical phenomena, and abstract ideas have been carved out as exceptions. *Bilski v. Kappos*, 561 U.S. ___, 130 S. Ct. 3218, 3225 (2010); *Chakrabarty*, 447 U.S. at 309. Section 101 is a "dynamic provision designed to encompass new and unforeseen inventions." *Bilski*, 130 S. Ct. at 3227 (quoting *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 135 (2001)).

Advances in the field of biotechnology fall squarely within the broad realm of "new and unforeseen inventions" contemplated by § 101. Nothing in the patent statute precludes the issuance of a patent on an isolated or purified product that has been derived from nature (including isolated DNA molecules) so long as it is distinct in "name, characteristic, and use" and it complies with the other patentability requirements. This distinction is critical, as all patentable things are products of nature in the sense that nature provides the basic source materials. *Merck & Co. v. Olin Mathieson*

Chem. Corp., 253 F.2d 156, 161-62 (4th Cir. 1958). The touchstone for patent eligibility flows from the differences in character between the isolated and native product, such differences being the product of human intervention. *See Chakrabarty*, 447 U.S. at 313 ("the relevant distinction [is] between products of nature . . . and human-made inventions"); *see also In re Bergy*, 596 F.2d 952, 976 (CCPA 1979) (recognizing that "a biologically pure culture produced by great labor in a laboratory and so claimed" is patent-eligible). Because the claimed isolated DNA molecules are distinct from their native counterparts and the result of human ingenuity, they are patent eligible.

III. The Court of Appeals' Decision Accords With The Settled Expectations Of Patent Owners.

Given the numerous risks associated with research and development, innovators must be able to rely on stable and consistent application of patent laws. *Bilski*, 130 S. Ct. at 3231 (Stevens, J., concurring) ("In the area of patents, it is especially important that the law remain stable and clear."); *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002) (citing *Warner Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17 (1997) and reiterating that "courts must be cautious before adopting changes that disrupt the settled expectations of the inventing community").

For decades, it has been accepted that compositions isolated from nature or purified beyond their natural state are patent-eligible. *See, e.g., In re Bergy*, 596 F.2d 952; *In re Kratz*, 592 F.2d 1169

(CCPA 1979); *In re Bergstrom*, 427 F.2d 1394 (CCPA 1970); *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95 (S.D.N.Y. 1911). The case law addressing important biotechnology inventions developed out of chemical patent case law.[3] There is no reason in principle why isolated DNA molecules and related applications should be treated differently from other human-made polymers or small molecules.

Indeed, the USPTO Utility Guidelines state this expressly: "Like other chemical compounds, DNA molecules are eligible for patents when isolated from their natural state and purified or when synthesized in a laboratory from chemical starting materials." USPTO Utility Guidelines, 66 Fed. Reg. 1093 (2001); *see also Carnegie Mellon Univ. v. Hoffmann-La Roche, Inc.*, 541 F.3d 1115, 1124 (Fed. Cir. 2008) (endorsing USPTO Written Description Guidelines as persuasive authority). In reliance on the settled principle that patent eligibility of isolated DNA molecules is no different than other chemical compounds, the USPTO has issued more than 50,000 patents directed to purified or isolated DNA, RNA, or amino acid sequences. *See* Subhashini Chandrasekharan & Robert Cook-Deegan, *Gene Patents and Personalized Medicine–What Lies Ahead?*, GENOME MED. 92 (2009).

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[3] *See, e.g.*, *Parke-Davis*, 189 F. at 95 (patentability of purified adrenaline extract); *Scripps Clinic and Res. Found. v. Genentech, Inc.*, 666 F. Supp. 1379 (N.D. Cal. 1987) (purified Factor VIII:C, a blood-clotting factor, patent-eligible under § 101); *In re Bergstrom*, 427 F.2d at 1394 (USPTO § 101 rejection of claims to substantially pure prostaglandin reversed).

Moreover, as this Court has recognized, § 101 is a threshold inquiry. *Bilski*, 130 S. Ct. at 3225. Assessing patent eligibility under § 101 is a prerequisite to considering the other legal requirements of patentability. *Parker v. Flook*, 437 U.S. 584, 593 (1978) ("The obligation to determine what type of discovery is sought to be patented must *precede* the determination of whether that discovery is, in fact, new or obvious.") (Emphasis added). Any claim failing the requirements of 35 U.S.C. § 101 must be rejected even if it meets all of the other legal requirements of patentability. *See In re Comiskey*, 499 F.3d 1365, 1371 (Fed. Cir. 2007) ("Only if the requirements of § 101 are satisfied is the inventor 'allowed to pass through to' the other requirements for patentability.").

For decades, courts have operated under this broad statutory framework, implicitly confirming the patent eligibility of isolated DNA sequences by addressing issues of novelty, obviousness, enablement, and written description with respect to countless patents claiming purified or isolated biological substances (including isolated DNA molecules)—issues these courts would not have reached if the inventions did not constitute patentable subject matter.[4] These cases, which turned on a range of non-threshold issues such as novelty and obviousness, lend support to the proposition that the threshold inquiry—patent eligibility—was satisfied. *See, e.g., SmithKline Beecham Corp. v. Apotex*, 403 F.3d 1331, 1352-55 (Fed. Cir. 2005) (holding that "a sua sponte inquiry into the patentability of the claimed subject matter is appropriate"); *In re Argoudelis*, 434 F.2d 1390, 1392 (CCPA 1970) (examining patent application to antibiotics extracted from strain of antibiotic-producing natural microorganism under 35 U.S.C. § 112).

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[4] *See, e.g.*, *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009); *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052 (Fed. Cir. 2005); *In re Wallach*, 378 F.3d 1330 (Fed. Cir. 2004) (claiming isolated DNA molecules encoding TNF binding proteins); *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200 (Fed. Cir. 1991) (claiming purified and isolated DNA sequence encoding (continued...)

Recognizing the substantial property rights involved, this Court should "be cautious before adopting changes that disrupt the settled expectations of the inventing community." *Festo Corp.*, 535 U.S. at 739 (citing *Warner Jenkinson*, 520 U.S. at 28).

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human erythropoietin); *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988); *In re Kratz*, 592 F.2d 1169 (CCPA 1979) (claiming substantially purified compound naturally-occurring in strawberries); *Merck & Co. v. Olin Mathieson Chem. Corp.*, 253 F.2d 156 (4th Cir. 1958) (claiming purified vitamin B_{12}); *Kuehmsted v. Farbenfabriken of Elberfield Co.*, 179 F. 701 (7th Cir. 1910) (claims to isolated, purified salicyclic acid); *Bergstrom*, 427 F.2d at 1394 (claiming purified prostaglandins); *Parke-Davis*, 189 F. at 95 (claiming isolated adrenaline).

IV. Without Strong Patent Protection, Innovation in the Area of Biotechnology Will Decline.

The U.S. patent system is based on the notion that *some* preemption of the claimed invention leads to greater progress for society by providing an incentive to would-be inventors to share their discoveries in exchange for a limited period of exclusivity. The reward of a patent grant is the right to exclude others. 35 U.S.C. § 154(a)(1) ("Every patent shall contain a short title of the invention and a grant to the patentee, his heirs or assigns, of the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States"). In *Mayo*, this Court acknowledged that patents by their very nature are preemptive:

> Patent protection is, after all, a two-edged sword. On the one hand, the promise of exclusive rights provides monetary incentives that lead to creation, invention, and discovery. On the other hand, that very exclusivity can impede the flow of information that might permit, indeed, spur invention, by, for example, raising the price of using the patented ideas once created.

Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. __, 132 S. Ct. 1289, 1305 (2012).

Congress has struck a carefully-crafted bargain, encouraging innovation and public disclosure in exchange for the exclusive rights conferred by a patent. *Bonito Boats, Inc., v. Thunder*

Craft Boats, Inc., 489 U.S. 141, 146 (1989). The strength of the U.S. patent system is essential to providing appropriate incentives for continued innovation, particularly in the area of biotechnology.

Over the past several decades, Congress has witnessed the USPTO grant thousands of patents claiming isolated DNA sequences. Even while this case was pending, Congress passed the Leahy-Smith America Invents Act. This Act reformed other important aspects of the patent system, but maintained the status quo with respect to the patent eligibility question presented here. *J.E.M. Ag Supply* is instructive on this point. In that case, this Court rejected the argument that plants did not fall within the scope of § 101. 534 U.S. 124, 144-45 (2001). In doing so, this Court relied in part on the fact that "the PTO has assigned utility patents for plants for at least 16 years, and there has been no indication from either Congress or agencies with expertise that such coverage is inconsistent with [federal law]." *Id.* at 144-45. As this Court has recognized, policy concerns regarding patent eligibility are best addressed by Congress, not the courts.

A. Patent Coverage Is Vital to Protect Investment in Research.

Drug and biologics development is one of the most research-intensive industries in the world. Innovators must search for the proverbial needle in the haystack. Creating a new medicine takes, on average, an investment of ten to fifteen years and over $1.2 billion.[5] Only two of ten marketed medicines return revenues that match or exceed the average costs of research and development. J.A. Vernon et al., *Drug Development Costs When Financial Risk Is Measured Using the Fama-French Three-Factor Model*, 19 HEALTH ECON. LETTERS 1002-1010 (2010). Patent protection provides innovators with limited exclusivity as an inducement to incur these enormous up-front costs and risks. Research, investment, and patent filing decisions must be made years in advance of marketing an FDA-approved product and as such, innovators in the field of biotechnology depend on a degree of certainty and predictability in patent law.

Patent protection of purified and isolated DNA compositions *increases* access to genetic diagnostic tests because the exclusivity conveyed in a patent grant provides the needed incentive to create the diagnostic tests in the first place. Without patent protection, the companies with the necessary expertise to develop those tests would lack incentive to undertake the enormous costs and risk associated with developing these breakthrough tests. This is especially so when contemplating the next generation of genetic diagnostic testing. Not only will it be more complex and costly to create than the first generation, but when coupled with increased clinical demands from FDA, companies could be dissuaded from investing the time and energy necessary to bring such a product to market.[6]

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[5] J. A. DiMasi & H.G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 467-79, 470 (2007); J. A. DiMasi & H.G. Grabowski, *Drug Discovery and Development: Understanding the R&D Process*, INNOVATION.ORG, 1-2, Feb. 2007.

Moreover, the mere fact that an invention is of great importance does not mandate its free and immediate availability to all humanity. On the contrary, highly valuable inventions historically have been granted patent protection.[7] Accordingly, patentability for a valuable biotechnology product should not be vitiated because of its perceived "expense" during a limited period of exclusivity. The benefit of public disclosure of the patented invention is immediate and long-term. In the face of the enormous risks and costs required to bring a biotechnology invention to patients, many life-saving products (that are now taken for granted) would not exist without the incentive of patent protection. Patent protection provides a limited period of exclusivity, but the therapeutic value of the claimed invention endures and is available for the benefit of future generations.

Finally, empirical evidence suggests that patenting does not limit research activity. According to one study, only one percent of academic respondents reported a project delay of more than a month due to patents on knowledge inputs necessary for their research; none reported abandoning a research project due to the existence of patents.[8]

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[6] *See* Christopher Holman, *Will Gene Patents Derail the Next-Generation of Genetic Technologies? A Reassessment of the Evidence Suggests Not*, 80 U. MO.-KAN. L.R. 563 (2012).

[7] *See, e.g.*, U.S. Patent No. 214,636 (Edison's light bulb); U.S. Patent No. 644,077 (to acetylsalicylic acid or "aspirin"); U.S. Patent No. 821,393 (Wright Brothers' flying machine).

B. Patents Spur Further Innovation.

In addition to providing incentives to companies to invest and innovate in the biotechnology field, patents serve an additional purpose of furthering innovation. For example, patent disclosures educate the research community on important advances and spark additional advancements. This exchange is efficient, allowing the public to learn from the successes and failures of others.

Protecting isolated DNA sequences spurs further progress in the area of biotechnology. In the absence of adequate patent protection, investments in innovation are subject to the "free-rider" problem in which copyists can take advantage of the pioneering work of others, stifling competition. Patents force these would-be copyists to "design around" the claimed invention, prompting competitors to develop new and potentially superior products that might otherwise have gone undeveloped if the competitors could simply copy the earlier invention during the patent term. Indeed, research and development continues to find alternative solutions and methods for screening and early detection of breast cancer.[9]

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[8] John P. Walsh et al., *Final Report to the National Academy of Sciences' Committee on Intellectual Property Rights in Genomic and Protein-Related Inventions: Patents, Material Transfers and Access to Research Inputs in Biomedical Research* (Sept. 20, 2005).

Patent owners have relied on the broad statutory framework for patent eligibility established by Congress, decades of jurisprudence reinforcing this framework and recognizing isolated and purified biological materials as patent-eligible subject matter, and the USPTO's longstanding policy and practice with respect to those inventions. The claimed isolated DNA sequences are tangible, human-made chemical compositions whose structure, function, utility, and informational content differ from their native counterparts. This Court should uphold the settled expectations and substantial property rights of innovators and clarify that although genes as they exist in the human body are not patent-eligible, human-made "isolated" DNA sequences are patent-eligible.

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[9] *See, e.g.*, Michelle Roberts, *Way to Spot Breast Cancer Years in Advance*, BBC NEWS (May 1, 2012), http://www.bbc.co.uk/news/health-17905601.

CONCLUSION

The judgment of the court of appeals should be affirmed.

Respectfully submitted,

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March 14, 2013

AMICUS CURIAE BRIEF

FILED

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No. 12-398

IN THE

Supreme Court of the United States

ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,
Petitioners,

v.

MYRIAD GENETICS, INC., ET AL.,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF FOR THE PHILADELPHIA INTELLECTUAL PROPERTY LAW ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENT MYRIAD GENETICS, INC.

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STATEMENT OF INTEREST OF *AMICUS CURIAE*

The Philadelphia Intellectual Property Law Association ("PIPLA") is a voluntary membership, non-profit organization of intellectual property law professionals and law student affiliates living or practicing within the geographical area of the Third Judicial Circuit. Among its purposes, the Association seeks to promote high standards of professional ethics, relationships and competency among its members, to enhance knowledge of intellectual property law and to enhance the development and administration of intellectual property law.[1]

In the record of this case and in much of the public discussion of the case, a great deal of emphasis has been placed on the alleged inhibition of research by the patents at issue. These issues concern PIPLA because they are often fodder for criticism of the patent system. Accordingly, PIPLA submits this brief to explain (i) why these allegations, and the evidence adduced to support those allegations, are misleading and, for the most part, irrelevant, and should therefore be disregarded, and (ii) why these allegations are exacerbated by the current state of case law surrounding the classic judicially created experimental use exception to patent infringement.

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[1] Pursuant to this Court's Rule 37.6, we note that no counsel for any party authored this brief, in whole or in part, nor did anyone other than the Philadelphia Intellectual Property Law Association and its counsel make any contribution, monetary or otherwise, to fund the preparation or submission of this brief. Petitioners have lodged a blanket consent to the filing of amicus briefs and a letter of consent from Respondents to the filing of this brief has been lodged with the Clerk of the Court.

STATEMENT OF THE CASE

The court has directed the parties to address a specific question. Effectively, that question is: assuming other conditions of patentability, such as novelty, non-obviousness, enablement and adequacy of claims, are met, can a human gene, isolated from its native environment, be patented? In this brief, the PIPLA takes no position on this question but urges that certain evidence submitted on behalf of petitioners should be disregarded.

SUMMARY OF ARGUMENT

Petitioners rely heavily on arguments that Myriad's patents inhibit research. Those arguments, and the evidence alleged to support them, prove nothing relevant to the central question to be addressed by the Court. Indeed those arguments and that evidence poison the Petitioners' argument, as well as much of the public discussion of this case. Those arguments and the evidence supporting them should therefore be disregarded.

The central question the Court has asked the parties to address is whether Myriad's patents claim exclusivity to subject matter that is not eligible to be patented because that subject matter is itself a law of nature or a natural substance rather than a practical application of a law of nature or a practical but modified form of a natural substance. In this brief, we take no position on that important question, but we urge the Court not to address it with Petitioner's irrelevant argument and equivocal evidence.

A patentee's right to exclude others from making, using or selling its claimed invention is beyond dispute. So too, is the impropriety of extending that exclusivity to laws of nature and naturally occurring substances. *See Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980). Patent exclusivity for *applications of* laws of nature and *significantly modified* natural substances is proper, however. *Id.* at 309-10.

This leads to the only question that the parties have been directed to address: Are human genes patentable?

As explicitly stated by Judge Lourie in the decision of the Federal Circuit,

> [This case] is not about whether individuals suspected of having an increased risk of developing breast cancer are entitled to a second opinion. Nor is it about whether the University of Utah, the owner of the instant patents, or Myriad, the exclusive licensee, has acted improperly in its licensing or enforcement policies with respect to the patents. The question is also not whether it is desirable for one company to hold a patent or license covering a test that may save people's lives, or for other companies to be excluded from the market encompassed by such a patent—that is the basic right provided by patent, *i.e.*, to exclude others from practicing the patented subject matter. It is also not whether the claims at issue are novel or

> nonobvious or too broad. Those questions are not before us.

Assoc. for Molecular Pathology, et al., v. United States Patent and Trademark Office, et al., __ F.3d __ (Fed. Cir. 2012) (slip op. at 37-38). Petitioners' Brief correctly states that

> The Court's seminal Section 101 cases describe three different ways to evaluate patents to determine whether they impermissibly claim natural phenomena: whether the patented composition has markedly different characteristics from any found in nature. [*Chakrabarty*, 447 U.S. at 309] at 310; whether the patent is based on an inventive concept, *Mayo*, 132 S. Ct. at 1294; and whether the patent preempts use of the underlying product or law of nature, foreclosing future innovation out of proportion with the patentee's contribution, *id.* at 1301-03.

Pet. Br. at 23-24. The relevance, if any, of the degree to which research or commercial use of the invention is impaired applies only to the third of these three methods of evaluation.

If the isolated BRCA1 and BRCA2 genes in this case are deemed to be not "markedly different" from their native form, that is the end of the inquiry, negating patent eligibility. A similar analysis may be made of the inventive concept inherent in the invention as claimed. If these analyses are not determinative, however, the degree to which research or commercial use of the "invention" forecloses future innovation should not be determined on the basis of the misleading and inconclusive arguments and evidence offered by Petitioners.

Petitioners broadly assert that research was inhibited by the patents at issue in this case. As discussed in Section I below, it is questionable whether the patents do in fact inhibit research and, in any event, the evidence asserted by Petitioners fails to prove that all research has been inhibited by the patents at issue here. This assertion therefore should be disregarded. Petitioners' arguments apparently are also based on an assumption, shared by certain of the declarants supporting those arguments, that patents can be used properly to preclude others from research to improve on, or to find alternatives to, or simply to evaluate the patented invention. To the contrary, classic patent law includes an experimental use exception that permits such research, as discussed in Section II below.

ARGUMENT

I. PETITIONERS' PREEMPTION ARGUMENTS SHOULD HAVE NO BEARING ON THE QUESTION OF PATENT ELIGIBILITY IN THIS CASE.

Petitioners describe a parade of horrors resulting from Myriad's patents on the isolated BRCA1 and BRCA2 genes. Petitioners, however, make no attempt to distinguish the limited exclusionary rights granted with these patents, properly enforced and interpreted, from an enormously exaggerated view of that exclusionary right, one that would preempt any and all activity related to the genes, both in and removed from their native environment. Any evidence of these alleged negative consequences is speculative and inconclusive at best, and serves only to cloud the real issue before the Court—whether Myriad's claims to the isolated BRCA1 and BRCA2 genes are, in fact, patent eligible.

As an initial matter, preemption should not be deemed a separate component of the patent eligibility analysis. At most, it is a secondary question that is relevant only if Myriad's isolated BRCA1 and BRCA2 molecules are held to be patent eligible subject matter. *See* Katherine J. Strandburg, *Much Ado About Preemption*, 50 Hous. L. Rev. 563, 613-614 (2012), available at http://www.houstonlawreview.org/wp-content/uploads/2013/02/7-Strandburg.pdf ("Preemption analysis was not central to any of the Court's determinations of how to apply per se patentable subject matter exclusions, nor, as we have seen, has it been particularly useful as a tool for analyzing potential overbroad downstream impact. Instead, the preemption rubric has served mainly to muddy the water and to distract from more pertinent questions.").

In this case, Petitioners barely address whether the inventors' first recognition of the significance of mutations in the claimed genes and subsequent isolation of those genes to enable the diagnostic tests which followed was in fact an inventive concept worthy of patent eligibility. Instead, Petitioners offer sweeping conclusions regarding the preemptive effect of Myriad's patents on gene research and medicine, such as that the patents reach "all uses of the two human genes" (Pet. Br. at 42) and "prevent and deter research" (*Id.* at 43). There is no direct support in the record for these and other of Petitioners' conclusions. Indeed, in many instances Petitioners make no attempt to offer any such support, much less tie the support they do cite to uses other than those which Myriad is entitled to exclude by the specific patent claims at issue.

Here, Petitioner's preemption arguments fall into two basic categories: (A) that the patents give Myriad an unrestricted monopoly on genes and testing procedures, and (B) that the patents generally impede research and innovation. As to the first category, the exclusive rights of patentees are restricted with respect to research on the patented invention. Consistent with this premise, the record gives no indication that Myriad's assertion of its patents represents a departure from long-standing and well-established principles of patent law granting patentees the right to exclude others from commercially exploiting their inventions for a limited period of time. As to the second category, contrary to Petitioners' claims, there is no conclusive evidence that Myriad's patents on the BRCA1 and BRCA2 genes impede or otherwise preempt research and innovation. In fact, the record suggests just the opposite.

A. Myriad's Assertion of Its Patents is Consistent With Existing Law.

Petitioners assert that "[b]ecause the patent claims reach all uses of the two human genes, Myriad has the authority to prevent all study of them." Pet. Br. at 42. That assertion is incorrect.

U.S. patent law recognizes experimentation on a patented invention to be excepted from activity that might otherwise be patent infringement. Notwithstanding certain decisions that may be inconsistent with the classic interpretation of that exception (as discussed in Section II below), Myriad cannot preempt all use or study of its inventions. Consistent with the classic experimental use exception recognized under U.S. case law, and as Myriad's President indicates, "[i]t has been, and still is, Myriad's policy and practice to allow scientists to conduct research studies on the BRCA1 and BRCA2 genes freely." JA 332 (Declaration of Gregory C. Critchfield, President of Myriad) ("Critchfield Declaration"); see also JA 623 ("I understand Myriad now asserts that it would never enforce its legal right to sue me for those actions if I were doing them for purely research purposes.").

Despite the experimental use exception and Myriad's stated policy of allowing research on the isolated genes covered by its claims, Petitioners suggest that Myriad's right to exclude has limited the number of other laboratories that provide the same diagnostic services as Myriad. Specifically, Petitioners claim that Myriad uses the challenged claims to prevent clinical testing at any other lab (Pet. Br. at 45), that Myriad prevents other laboratories from providing diagnostic testing at a lower price (*Id.*), and that Myriad's monopoly on the BRCA genes prevents other laboratories from including these genes when clinically assaying other genes. *Id.* at 46. To the extent the Court focuses on the issue of preemption, these facts are not relevant to that issue absent objective evidence of the commercial versus experimental nature of the activity.

Here, in return for disclosing its inventions to the public, Myriad obtained a time-limited right to commercialize those inventions. Thereafter these inventions are donated to the public to freely use. *See Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 63 (1998) (noting that a patent represents "a carefully crafted bargain" in which the patentee is granted "an exclusive monopoly for a limited period of time" in exchange for "the public disclosure" of a new invention). This bargain entitles a patentee to assert its patent against commercial exploitation of the invention, as appears to have been the case with respect to Myriad's efforts to curb other diagnostic labs, including some of the Petitioners', from commercially exploiting its patents. These efforts are referred to in at least one of the declarations submitted by Petitioners. JA 341-342; JA 156 ("[W]e were charging patients less than Myriad was charging. If we, or another laboratory, were to begin offering such genetic testing again, I believe that it would be offered at a price significantly lower than Myriad's current pricing for the same or similar testing."). Myriad's efforts to enforce its patents against unauthorized third party commercial use should have no bearing on patent eligibility.

The patent laws were developed to protect this very right of a patentee to exclude others from engaging in this type of commercial activity for a limited time. Accordingly, the negative downstream commercial effects described by Petitioners are not the proper focus of any kind of preemption inquiry since it is an effect that results from almost every patent granted.

Petitioners' preemption arguments are exaggerated in any event. To the extent Petitioners or third parties have refrained from providing BRCA diagnostic testing services, it is unclear whether the services they claim to be foregoing are for profit or are non-commercial in nature, or whether the services they provide would even infringe Myriad's rights. Petitioners do not specify. As for Myriad dictating a "standard" of testing (*see* Pet. Br. at 46), as at least one other Amicus pointed out, alternate methodologies for sequencing DNA are available, including "revolutionary next-generation technologies capable of determining the sequence of single molecules, without necessitating any isolation of specific DNA sequences." Brief of Amicus Curiae Law Professor Christopher M. Holman in Support of Neither Party at 13-14, *Association for Molecular Pathology v. United States Patent & Trademark Office* et al., 689 F.3d 1303 (Fed. Cir. 2012) 2012 WL 2884112, at *13-15.

Rather than address these points head on, Petitioners gloss over them in favor of blanket assumptions as to the preemptive impact of Myriad's patents on genetic testing. The Court should disregard Petitioners' assumptions regarding preemption in assessing the patentability of Myriad's claims. *See* Strandburg, 50 Hous. L. Rev. at 568 (Preemption "has been over-emphasized and mischaracterized. Per se exclusions, and their theoretical justifications, deserve more attention.").

B. The Record Does Not Support Petitioners' Claim that Myriad's Patents Impede Research and Innovation.

One of the cornerstones of Petitioners' preemption argument is the idea that the Myriad patents have somehow "prevent[ed] and deter[red] research." Pet. Br. at 43. In support of this proposition, Petitioners cite an example of Myriad asserting its patent rights against a third party who used the claimed invention in the course of paid research. JA 257-58. According to the Critchfield Declaration, however, this third party, an acknowledged competitor of Myriad, was supplying its diagnostic testing services commercially, although in support of undefined research protocols. JA 341-42 (noting that the purpose of Myriad's enforcement efforts was to request third parties to "cease their commercial diagnostic testing"); *see also* JA 257. There is no indication whether the associated "research protocols" involved research on the relevant genes or related diagnostic or therapeutic methods, much less whether activity in support of that research would have qualified as excepted experimental activity. In any event, such broadly described examples are hardly evidence that Myriad's patents impaired legitimate research.

Petitioners' other evidence on the issue of preemption is similarly equivocal. By way of example, Petitioners cite to a survey finding that some labs "decid[ed] not to develop a new clinical genetic test because of a gene patent or license." Pet. Br. at 43. The fact that a survey respondent elected not to develop a new clinical test because of a gene patent or license, however, hardly suggests that Myriad's patents actually impaired research and innovation. Indeed, research to develop an improved test may well fit within a properly defined experimental use exception.

If anything, the record shows that with respect to gene patents, firms and research organizations in the United States have developed "'working solutions' which allow them to continue to innovate relatively unimpeded." JA 574-75 (December 23, 2009 Declaration of Joseph Straus, Director Emeritus of the Max-Planck-Institute for Intellectual Property, Competition and Tax Law, Munich) (commenting on a study showing that working solutions included license negotiations where necessary or the avoidance of patent obstacles by working around the claims). Other research shows that academics focusing on biomedical research rarely pay much attention to the others' patents. And for those researchers who have become aware of others' patents, survey evidence indicates that very few, if any, have abandoned or altered their research due to such patents. *Id.*

Far from having a stifling effect on research, the record shows that gene patents may encourage and foster innovation. According to the Critchfield Declaration, since Myriad's disclosure of the BRCA1 and BRCA2 isolated genes, at least 18,000 researchers have conducted studies on them, and scientists have published over 8,000 reports relating to them. JA 336-37 (noting that "many of these scientists are members of the institutional Plaintiffs in this suit including the Association for Molecular Pathology, American College of Medical Genetics, American Society for Clinical Pathology, and College of American Pathologists). In addition, there have been over 130 clinical trials commenced on the BRCA1 and BRCA2 genes. *Id.* Thus, contrary to Petitioners' claims, it is clear that gene patents, such as those at issue here, do not necessarily pose an obstacle to scientific research.

Evidence of Myriad's patents blocking academic research is also lacking. As one of the Petitioners freely admitted, she "sequence[s] human genes, including the BRCA1 and BRCA2 genes for research subjects in [her] research lab" and has been doing so unimpeded. JA 59. This is consistent with Myriad's stated policy of allowing scientists to conduct research studies on the BRCA1 and BRCA2 genes freely.

It bears noting that in one of the first cases involving patentability of genetic organisms, the Court predicted "[t]he grant or denial of patents ... is not likely to put an end to genetic research ...[and that] patentability will not deter the scientific mind from probing into the unknown .... Whether respondent's claims are patentable may determine whether research efforts are accelerated by the hope of reward or slowed by want of incentives, but that is all." *Chakrabarty*, 447 U.S. at 317. The Court's observation in *Chakrabarty* remains true today.

As a general matter, biotechnology patents have not had a substantial impact upon academic research. In fact, in one study "only about 1% of the random sample of academics reported experiencing a delay or modification in their research due to patents." John P. Walsh. et al., *Patents, Material Transfers and Access to Research Inputs in Biomedical Research*, Final Report to the National

Academy of Sciences' Committee on Intellectual Property Rights in Genomic and Protein-Related Inventions, 37 (2005), available at www2.druid.dk/conferences/viewpaper.php?id=776&cf=8. In a more recent study, strikingly few documented examples were found in which the fears surrounding gene patents manifested themselves. Christopher M. Holman, *The Impact of Human Gene Patents on Innovation and Access: A Survey of Human Gene Patent Litigation*, 76 UMKC L. Rev. 295, 299-300 (2007), available at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1090562.

Petitioner's evidence concerning research preemption is at best inconclusive. For example, the same report Petitioner cites for the proposition that gene patent law "threatens medical progress" (Pet. Br. at 42) found the following:

> The case studies and literature review support . . . assertions that patents attract investment to fund genetic research. Both the case studies and literature review reveal that when researchers or companies sought private funds to initiate or advance their genetic research, investors were willing to provide funding because of the prospect of patents being granted as a result of the research. For example, according to a policy paper, Eli Lilly agreed to fund Myriad Genetics' ongoing efforts to find genes associated with breast cancer "in return for licensing privileges for diagnostic kits and therapeutic

> products on BRCA1." This agreement was based on the assumption that Myriad would in fact be the first to discover the gene and that the company would then patent the gene. The rights promised to Eli Lilly would then be derived from that patent.

Rep of the Sec'y's Advisory Comm. on Genetics, Health, & Soc'y, HHS, *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests* 23 ("SACGHS Report") (2010) (footnote omitted), *available at* http://oba.od.nih.gov/oba/sacghs/reports/sacghs_patents_report_2010.pdf. "In the case of genetic testing companies, the limited period of exclusivity provided by a patent is almost always required to secure sufficient capital needed to establish testing capability on a clinical scale." JA 448.

Petitioners cite the cost of Myriad's BRCA1 and BRCA2 testing as impeding patient access to diagnostic testing. However, patents such as Myriad's appear to have little, if any, monopolistic effect on the price of diagnostic tests. *See* Robert Cook-Deegan, et al., *Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers with Colon Cancers*, 12 Genetics Med. S15, S23-24 (2010), available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3047448/.

Regarding Petitioners' assertions of problems associated with "second opinion" molecular genetic testing as a result of Myriad's patents, the Critchfield Declaration suggests the contrary. JA

364-65 (Multiple laboratories provide second opinions regarding BRCA1 and BRCA2 test results). The only conclusive evidence of patient access being limited relates to instances where insurance coverage for a particular test was unavailable. In fact, according to the Critchfield Declaration more than 90% of Myriad's BRCAnalysis® tests ordered by healthcare providers are covered by insurance, and the average reimbursement rate is over 90% of the cost of the test. JA366-67. There are also more than 2,600 insurance payors who reimburse for the BRCAnalysis® test. *Id.*

The evidence of record falls far short of proving that Myriad's patents inhibit research and innovation. Rather, the record indicates that Myriad has allowed and continues to allow non-commercial research on the BRCA1 and BRCA2 genes freely. Many researchers acknowledge that they have never been contacted by Myriad and that neither the patents at issue in this suit nor Myriad have in any way hampered such research. JA302-04 (December 23, 2009 Declaration of Richard Baer, Ph.D., Professor of Pathology & Cell Biology, Columbia University) (noting that his research involved, *inter alia*, "plasmids containing BRCA1 cDNA, heterologous cells expressing BRCA1 protein, primers designed to PCR amplify BRCA1 cDNA, and antibodies against BRCA1 protein"); JA 311-14 (December 23, 2009 Declaration of Rong Li, Ph.D, Professor, Department of Molecular Medicine/ Institute of Biotechnology at the University of Texas Health Science Center) (noting same). Ultimately, there is little evidence that any research Petitioners seek to conduct would be prohibited by the patents in suit.

II. MUCH OF THE RESEARCH ACTIVITY ALLEGEDLY CURTAILED IN DEFERENCE TO THE MYRIAD PATENTS CAN BE TRACED TO A MISGUIDED VIEW OF U.S. PATENT LAW.

Scientists generally, and particularly those involved in this case along with Myriad and its inventors, are constrained by questionable case law regarding what may be referred to as the experimental use exception to patent infringement. Research possibly leading to improvements on, or alternatives to, a patented invention, should be exempt from claims of patent infringement under classic U.S. patent law, just as certain uses of copyrighted material is exempt from infringement as "fair use," and for the same reason. 17 U.S.C. § 107 (1992). *See Campbell v. Acuff-Rose Music*, 510 U.S. 569, 575 (1994) ("From the infancy of copyright protection, some opportunity for fair use of copyrighted materials has been thought necessary to fulfill copyright's very purpose '[t]o promote the Progress of Science and useful Arts'"). Indeed, patent law recognizes an exemption for experimentation on an invention. Unfortunately, the current state of the case law may lead to a different conclusion with respect to experimentation not limited to philosophical purposes only.

To the extent any patent evaluation, or search for alternatives or improvements, may have been inhibited in connection with the patents in suit here, that is an unfortunate consequence of the uncertainty in the law, for which Myriad should not be held accountable.

As discussed more fully below, the exception for experimental use of an invention dates back in U.S. case law nearly two hundred years. But when the U.S. common law of patents was codified in 1952, no provision was included that recognized this exemption. Subsequent case law recognized the exemption but progressively interpreted it more narrowly. Calls for Congressional or judicial correction of this narrow interpretation have gone unheeded.

The experimental use exception originated in 1813 with an opinion by Supreme Court Justice Joseph Story. Applying the common law of patents to render a decision in favor of an accused infringer, Justice Story stated that they provided no remedy where the alleged infringement was "merely for philosophical experiments, or for the purpose of ascertaining the sufficiency of the machine to produce its described effects." *Whittemore v. Cutter*, 29 F. Cas. 1120, 1121 (C.C.D. Mass. 1813) (No. 17,600). Justice Story elaborated on that position shortly afterward, claiming that a finding of infringement required "an intent to infringe the patent-right, and deprive the owner of the lawful rewards of his discovery." *Sawin v. Guild*, 21 F. Cas. 554, 555 (C.C.D. Mass. 1813) (No. 12,391). Taken together, those statements crafted a relatively broad infringement defense that covered the use of a patented invention provided the use did not usurp the benefits afforded to the inventor by the patent system.

As originally set forth by Justice Story in *Whittemore*, the defense included two distinct activities. First, it covered "philosophical experiments," by which Justice Story presumably referred to acts of scientific inquiry. But it also covered actions taken "for the purpose of ascertaining the sufficiency of the machine to produce its described effects." The distinction is critical. While the former protects general acts of research for philosophical purposes only, the latter explicitly protects the actual use of an invention when such activity would otherwise fall squarely within the scope of infringement, provided the use is to verify the ability of the claimed invention to function as claimed. Thus properly excepted experimental uses were not limited to uses for philosophical inquiry only.

The purpose of that broad experimental use exception fit comfortably within the framework of the country's nascent patent laws by promoting further innovation. By 1890, it was well-settled that the exception provided a safe harbor for certain alleged acts of infringement. Yale University Professor William C. Robinson, in his seminal treatise, The Law of Patents for Useful Inventions, emphasized that:

> The interest to be promoted by the wrongful employment of the invention must be hostile to the interest of the patentee. The interest of the patentee is represented by the emoluments which he does or might receive from the practice of the invention by himself or others. These, though not always taking the shape of money, are of a pecuniary character, and their value is capable of estimation like other property. Hence acts of infringement must attack the right of the patentee to these

> emoluments, and either turn them aside into other channels or prevent them from accruing in favor of any one.

W. Robinson, The Law of Patents for Useful Inventions, § 898 (1890). Robinson went on to qualify this generalization, however:

> [W]here [an alleged infringement] is made or used as an experiment, whether for the gratification of scientific tastes, or for curiosity, or for amusement, the interests of the patentee are not antagonized, the sole effect being of an intellectual character in the promotion of the employer's knowledge or the relaxation afforded to his mind.

Id. This qualification may have engendered the emphasis on the commerciality of uses not encompassed by the exception, as the exception was interpreted in the second half of the twentieth century.

In 1935, a district court citing Robinson applied the exception in favor of a university that was using patented machine parts, finding that the parts were used only in laboratory experiments. *See Ruth v. Stearns-Roger Mfg. Co.*, 13 F. Supp. 697, 703, 713 (D. Colo. 1935). The exception, however, did not cover similar parts sold commercially. *Id.* at 713. Another court found that the exception protected research and testing on a product performed before the defendant put the product into commercial production. *See Akro Agate Co. v. Master Marble Co.*, 18 F. Supp. 305, 333 (N.D. W. Va. 1937). Yet another held that an accused device did not infringe because the defendant did not manufacture it for sale. *See Dugan v. Lear Avia*, 55 F. Supp. 223, 229 (S.D.N.Y. 1944).

Initially, the Court of Claims, predecessor to the Federal Circuit, continued to focus on the experimental nature of the alleged use and twice applied the exception to find non-infringement. In 1958, it held that the government's use of a patented heat-resistant alloy was not an infringement when it was used only for testing. *See Chesterfield v. United States*, 159 F. Supp. 371, 376 (Ct. Cl. 1958). Then, in 1975, it held that exception covered NASA's use of a patented glove during a training experiment. *See Finney v. United States*, 188 U.S.P.Q. 33, 35 (Ct. Cl. Trial Div. 1975). Soon afterward, however, the analyses of the Court of Claims, and then the Federal Circuit, shifted.

Just one year after its decision in *Finney*, the Court of Claims began to narrow the exception. In *Pitcairn v. United States*, the court ruled that the federal government's use of patented helicopter rotors for "tests, demonstrations, and experiments" of its helicopters did not fall within the scope of the exception because those uses were "in keeping with the legitimate business of the using agency." *Pitcairn v. United States*, 547 F.2d 1106, 1125-26 (Ct. Cl. 1976). Thus, instead of analyzing the commercial aspect of the claimed experimental use, the court applied a narrower "legitimate business" test that disregarded whether the use in fact deprived the patentee of any benefit to which it was entitled.

The Federal Circuit used that new analysis in 1984, when it was asked to extend the classic experimental use exception to the activity of a generic drug manufacturer's activity to prepare to make and sell a patented drug following expiration of a patent covering the drug. *Roche Products, Inc. v. Bolar Pharmaceutical Co.*, 733 F.2d 858 (Fed. Cir. 1984), *cert. denied*, 469 U.S. 856 (1984). In refusing to do so, the court relied on the defendant's intent to profit from their activity *in the future* as sufficient commercial activity to remove that activity from the ambit of the experimental use exception *Id.* at 863. [2]

The Federal Circuit subsequently narrowed the judicially-created experimental use exception even further when asked to extend it to any research by a public research institution. *Madey v. Duke Univ.*, 307 F.3d 1351, 1361-62 (Fed. Cir. 2002). According to the court, Duke University's status as a non-profit institution did not protect its use of a patented laser for experimental research purposes because research *was* the university's business. *Id.* at 1362. Although Duke University did not contend that its research was *on the patented laser*, its effort to extend the experimental use exemption to cover *use of the laser in other research* led the court to narrow the exception in a manner that would seem to disentitle any experimental use of an invention that had any commercial implication whatsoever, irrespective of even the use originally included by Justice Story in the original statement of the experimental use exemption. As set forth in *Madey*:

> Our precedent clearly does not immunize use that is in any way

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[2] Congress responded to the Federal Circuit's *Roche Products v. Bolar* decision with an amendment of the Hatch-Waxman Act, legislatively exempting such activity as it related to FDA regulatory approval. Drug Price Competition and Patent Term Restoration Act, PL 98-417, 98 Stat 1585 (1984); Patent Act, 35 USC §271(1) (1984) (discussed *infra*).

> commercial in nature. Similarly, our precedent does not immunize any conduct that is in keeping with the alleged infringer's legitimate business, regardless of commercial implications. For example, major research universities, such as Duke, often sanction and fund research projects with arguably no commercial application whatsoever. However, these projects unmistakably further the institution's legitimate business objectives, including educating and enlightening students and faculty participating in these projects. These projects also serve, for example, to increase the status of the institution and lure lucrative research grants, students and faculty.
>
> In short, regardless of whether a particular institution or entity is engaged in an endeavor for commercial gain, so long as the act is in furtherance of the alleged infringer's legitimate business and is not solely for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry, the act does not qualify for the very narrow and strictly limited experimental use defense. Moreover, the profit or non-profit status of the user is not determinative.

Id.

That narrow application of the judicially-created experimental use exception is cast in sharp relief when compared to the broad interpretation of the legislatively-created safe harbor provision of the Hatch-Waxman Act by both the Supreme Court, *Merck KGaA v. Integra LifeSciences, Ltd.,* 545 U.S. 193 (2005) and the Federal Circuit, *Integra LifeSciences Ltd. v. Merck KGaA,* 331 F.3d 860 (2003) (on remand, 496 F.3d 1334 (2007)) and *Momenta Pharmaceuticals v. Amphastar Pharmaceuticals,* 686 F.3d 1348 (Fed. Cir. 2012).

Relative to the judicially-created experimental use exception, the *Integra LifeSciences* case is notable for the fact that patentee/plaintiff did not even appeal the district court finding that certain experimental activity of the accused infringer (clearly a for-profit entity) was protected by the judicially-created experimental use exception. In writing for the Court, Justice Scalia noted this without comment. 545 U.S. at 197, n.3.

While the majority of the Federal Circuit panel in that court's first decision in *Integra LifeSciences* favored a more narrow reading of the Hatch-Waxman legislative exemption, Judge Pauline Newman registered a strong dissent, urging application of the judicially-created experimental use exception even to activity that the district court had found to be an infringement. In that dissent, Judge Newman articulated both the history of, and the policy justification for, the judicially-created experimental use exception. 331 F.3d 860, 866 (Fed. Cir. 2003).

In her sharply-worded dissent, Judge Newman accused the majority of eliminating the judicially-created experimental use exception altogether, contrary to established precedent and policy. *Id.* at 875. The consequence of the majority's opinion, according to Judge Newman, would be to place all information disclosed through the patent system "on ice," allowing a patentee to "bar not only patent-protected competition, but all research that might lead to competition, as well as barring improvement or challenge or avoidance of patented technology," thereby halting the advance of technology. *Id.* As for the case itself, Judge Newman indicated the activities in question constituted research into patented science and technology, which she deemed to be protected by the experimental use exception. *Id.* at 878.

More recently, Judge Newman, writing for a panel majority in which Judge S. Jay Plager concurred, again noted that broadened view of the experimental use exception. *See In re Rosuvastatin Calcium Patent Litigation*, __ F.3d __, 2012 WL 6217356, at *12 (Fed. Cir. December 14, 2012) ("[P]atenting does not deprive the public of the right to experiment with and improve upon the patented subject matter.")

The need for clarification of the law regarding the experimental use exception has been recognized by others. After an historic study of the U.S. patent system, a National Academies Report identified several "performance criteria [of the system] that are widely thought to be important if not necessary conditions for innovation," one of which specifically targeted the problem identified in the *Madey* decision.

> In light of the Federal Circuit's 2002 ruling that even non-commercial scientific research conducted in a university enjoys no protection from patent infringement liability [implicitly referring to *Madey*] and in view of the degree to which the academic research community especially has proceeded with their work in the belief that such an exception existed, there should be limited protection for some research uses of patent inventions.

Executive Summary: A Patent System For the 21st Century, page 7.[3]

Other academic studies have reached similar conclusions: "[O]ver time, the focus of the inquiry shifted from whether the alleged infringing use was for profit or financial gain to whether it furthered one's legitimate business interests (regardless of profit)." Elizabeth A. Rowe, *The Experimental Use Exception to Patent Infringement: Do Universities Deserve Special Treatment?*, 57 Hastings L.J. 921, 926 (2006), *available at* http://scholarship.law.ufl.edu/facultypub/91. See also Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. Chi. L. Rev. 1017, 1086 (1989) ("[A]s the line between basic and applied research becomes blurred in certain fields, patent protection increasingly threatens to encroach on the domain of research science, making it necessary to work out an accommodation between the two perspectives. A carefully formulated experimental use exemption from patent infringement liability is an important first step in that direction.").

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[3] Report of the Committee on Intellectual Property Rights in the Knowledge-Based Economy, Board on Science, Technology, and Economic Policy and Global Affairs Division of the National Research Council of the National Academies, available at http://www.nap.edu/openbook.php?isbn=0309089107.

The uncertain status of the judicially-created experimental use exception and the acknowledged need to revisit (or legislatively redefine) the extent of that exception is harmful to innovation because it provides cover for the efforts of those seeking to discredit the patent system generally, and the Myriad patents specifically.

CONCLUSION

For the foregoing reasons, Amicus Philadelphia Intellectual Property Law Association urges the Court, in reaching its decision on the patent eligibility of the patents at issue here, to disregard, as irrelevant and inconclusive, all arguments (and supporting evidence) that the patents at issue have inhibited or will inhibit. research.

Respectfully submitted,

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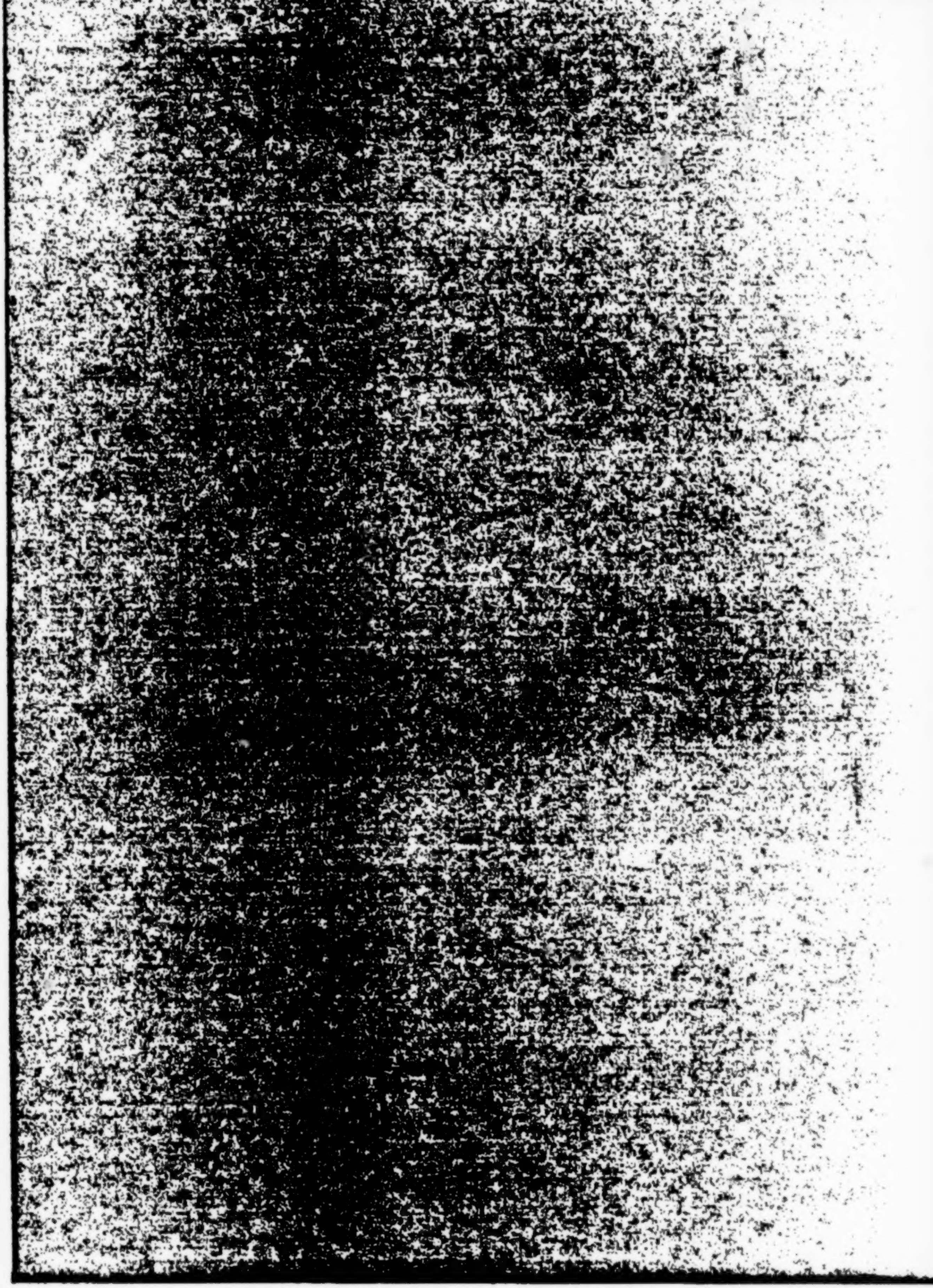

AMICUS
CURIAE
BRIEF

Supreme Court, U.S.
FILED

JAN 31 2013

OFFICE OF THE CLERK

No. 12-398

IN THE
Supreme Court of the United States

ASSOCIATION FOR MOLECULAR PATHOLOGY,
et al.
Petitioners,
v.
MYRIAD GENETICS INC. et al.
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

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BRIEF OF AMICUS CURIAE SIGRAM SCHINDLER BETEILIGUNGSGESELLSCHAFT mbH, IN SUPPORT OF NEITHER PARTY

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STATEMENT OF IDENTITY AND INTEREST

Sigram Schindler Beteiligungsgesellschaft mbH and its subsidiaries (collectively "SSBG") are research-based high technology companies located in Berlin, Germany, developing and selling products and services all over the world, including the US, via TELES AG. SSBG is a majority shareholder of TELES AG, founded by Sigram Schindler, at that time full professor at the Technical University of Berlin's Computer Sciences Department [1]

SSBG's ability to invest in high-tech research is dependent upon the intellectual property protections accorded under the global patent systems, in particular in the United States and Europe. Strong patent systems require that the patents issued are consistently interpreted so that the metes and bound of the protected subject matter is clear and consistent. SSGB, therefore, has a vested interest in supporting the US patent system in its on-going development in adjusting itself to the needs of sectors of the economy based on emerging technologies. This court provided clear guidance and mandates in the *KSR/Bilski/Mayo* line of decisions to further advance US patent precedence in this area

This brief, in support of neither party, is filed on behalf of *Amicus Curiae* SSBG – which has no financial interest in either side.

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[1] Pursuant to Supreme Court Rule 37.6, amicus curiae states that no counsel for a party authored this brief in whole or in part, and no entity or person other than amicus curiae, its members, and its counsel, made any monetary contribution toward the preparation or submission of this brief. Letters from the parties consenting to the filing of this brief are on file with the Clerk.

SUMMARY OF THE ARGUMENT

This Amicus Brief aims at contributing – to the dispute of patent-eligibility of the human genome – the view on it of advanced IT/epistemology/mathematics/physics, as developed in SSBG's interdisciplinary FSTP project.

This contribution suggests deciding the question by applying a test to such an invention. This test checks whether it functionally is defined precisely or it is only an abstract idea – implying, this invention also has a fuzzy if not undecidable scope. The author has recently submitted this "not only abstract idea" test in an Amicus Brief to the CAFC which had asked for such a test for a "computer-implemented" invention.

The subsequent section starts by presenting that it is reasonable to approach the patent-eligibility problem of the human genome – given the very thoughtful but equally controversial discussion of this issue – by avoiding stating speculative facts of fundamental physics and instead trying to bring consensus into this discussion.

Such a solution of this problem would enable granting very strong and stable patents for human genome based inventions – yet only if the scope of protection granted to the invention is so clearly defined that it cannot preempt research and/or innovations outsides of the scope of protection granted. Academic research ought not to be hindered by patents at all – at least relating to the human genome.

The requirement to be clearly understood – to be met particularly by the scope of protection granted to such an invention, i.e. not by the physical realization of the human genome's functionalities – implies a serious limitation as to the "philosophy" of specifying the claimed invention, explained in detail by the next sections.

In principle, this limitation is necessary for warranting that a claimed invention, once it passed the 35 U.S.C. § 112 test in an unquestionable way, would also make the 35 U.S.C. §§ 102, 103, 101 tests easy – i.e. avoid undecidability as to any one of them. Testing a claimed invention as to these four sections in a different sequence is problematic, anyway.

Particularly striking is that – as to patent-eligibility of the human genome – the suggested test makes the existing conflict over the human genome obsolete: While it indicates the human genome to be patent-non-eligible, it also indicates commercially equivalent human genome based inventions patent-eligible. As a result, such patents even would be significantly stronger.

Finally, if a human genome based invention passes this not only abstract idea test, it – by logical implication of the definition of this test – also is non-preemptive, i.e. its scope of protection by US patent law is limited to exactly this well-defined scope. This aspect of the non abstract idea test, namely its side effect of checking the invention for non-preemption, was not stressed in our CAFC Amicus Brief, as it was not really material in the *CLS* case.

ARGUMENT

I. PATENT PRECEDENTS SHOULD AVOID FUNDAMENTAL PHYSICS

With its *KSR* and *Bilski* decisions, and in particular with its *Mayo* decision, this court clearly demanded that the US patent precedents cater also to needs of sectors of the economy based on emerging technologies. Many of them are often "(fictional) model" based – in contrast to MoT based – e.g. gene technology. But should such models comprise speculative notions of fundamental physics?

The human genome is a fictional model relating a man's traits and genes. It is inherently based on speculative fundamental physics notions – e.g. the physical forces bonding atoms together to molecules, or these molecules'/genes' physical encodings of their geno-/pheno-type relational potentials – which patent precedents hitherto abstracted away. But this abstraction recently has been abandoned, and human genome based patent precedents started to tamper with the human genome model's fundamental physics realization. Due to the latter's above described uncertainties, such patent precedents cannot be sure that e.g. some "physically isolated" gene does not exist in nature, or its "physical isolation" does create anything functionally new.

Sections II-IV show: Human genome based patent precedents need not deal with uncertainties of fundamental physics. It may stay in the world of creating/describing such inventions in the language of the person of ordinary skill in genetics.

But first **a)** and **b)** explain the two above exemplary risks inherent to using fundamental physics in human genome based genetics.

a) First of all, one day it may turn out that this isolated gene exists in nature. But even if not: Then physically there still is doubt about the being of the physical forces gluing atoms together to extremely complicated molecules such as the human DNA ones. I.e.: The meaning of the term “isolating” such a complicated gene needs clarification. Namely: Is this isolation really a man’s intentional creation to be represented by an “inventive concept”[3),III.2Def1,ftn4)]? If this isolation is achieved by just using a “natural phenomenon”, then it is not subject to patent-eligibility in the US, up to this court.

There is a viable argument that molecular biology here indeed uses in a known way a natural phenomenon (not really understood). The reason being that molecular biology as to such questions must blindly trust bio-chemistry, which must blindly trust physical chemistry, which must blindly trust fundamental physics, which uses mathematics for fabricating different models allegedly answering such questions as to atoms’/molecules’ electromagnetic affinities to each other enabling the formation of the large and diversified human genome (actually observable by visible light wave-length microscopes) and hence as to isolating its genes. Thereby the exact reasons of such affinities and hence implications of such an isolation – assumed, in any such model, always based on the individual atoms'/molecules' electrons for explaining the molecular binding forces between them – are and will remain unknown on the atomic level as their components as such, e.g. electrons, are not observable (see Heisenberg's "uncertainty relation"). One of the godfathers of physical chemistry, Linus Pauling, never claimed that he was considering these bonding forces as something other than a natural phenomenon, for which to analyse he used a knowingly speculative fundamental physics model, namely that of Nils Bohr, which rightfully still is used in biochemistry. In fundamental physics meanwhile Bohr's atom model is replaced by Schrödinger's model and then by quantum field theoretical models.

This implies the question, whether leveraging on such a speculative fundamental physics model underlying a "natural phenomenon" by known means developed to this end – "just applying it" for gene isolation, as this court referred to in its *Mayo* decision – is patent-eligible.

b) In view of **a)** the question exists, whether the physical isolation as such of a gene would not make it non-patent-eligible. This problem might be fixed only if its biological functionality were new, at least. But this argument also is barred if the claimed invention assumes (as regularly is the case) that its isolation has no impact on its functionality; otherwise clarifying **b)** needs some more words but arrives at the same end – due to the obscurity of the physical encoding of the human genome's biological functionality.

To summarize **a)** and **b)**: Fundamentals of physics in human genome patent precedents introduce into it their uncertainties. Hence, they prevent granting dependable patents in this field – as they expose their inventions to legitimate attacks by all kinds of physical theories.

But dependable human genome based patents are indispensable for stimulating research in such technologies – for sake of the overwhelming humanitarian benefits they undoubtedly embody – by making such research also economically interesting. After all, this was and is the primary social justification of patent law: This is an issue of all overarching importance – clearly not an all overruling one.

That, independent of the above physical fundamentals, dependable human genome based patents can be granted in a responsible manner, as demanded by this court, is explained in the next sections. They will show that this requires in particular that these patents' scopes are "well-defined". This is a mathematical term from the early 20th century when the scientific foundations of mathematics had to be cleaned up and hence had often to be stated "the definition used is already cleaned-up", i.e. from a period of time in which mathematics learned that it then partially was built on sand. This insight currently comes up in "model based" patent precedents, too – taking it to a higher level of evolution as well (as explained in[3),*]).

In total: The broadly known and vastly mental DNA model of the human genome – not aiming at clarifying how fundamental physics enables it, but backed-up by much biological and legal experience with it – is a clear and sufficient legal basis under society's control. Expanding it to comprise fundamental physics models is legally not needed by patent precedents and, in fact, exposes it to incalculable risks.

II. THE 'NON ABSTRACT IDEA' TEST OF THE HUMAN GENOME AND OF A HUMAN GENOME BASED INVENTION

A PTO's or court's decision as to a human genome based claimed invention (i.e. not focusing just on the human genome) needs of its inventive steps only their descriptions by creative/inventive concepts, of which none needs to refer to a physical modification of a physical human gene. All such references – by independent inventive concepts embodying this invention over prior art – in the patent's specification and the respective claim's wording need to address only the model world of biological chemistry and hence are next-to-trivial. And this also holds for the "non abstract idea" test of a human genome based invention. But: This test requires the patent disclosing the invention to specify also **the practical problem it solves** as well as **its simple independent inventive concepts**[2].

This test of an invention – for it not to be an "abstract idea" – has two steps:

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[2] In patent language the terms "invention", "system", method", "solution", "problem", ... stand for "type"- alias "class"-kind notions, as called in IT.

1) Disaggregating the claimed invention's inventive compound concept(s) into its(their) said simple independent inventive concepts,
2) Verifying that – if the invention is reduced by a property described by at least one of said concepts of 1) – performing this reduced invention does not solve the problem.

A patent granted for an invention with a so defined scope of protection logically cannot preempt any innovation outside of this scope.

By its so defined "no abstract idea" test of the human genome, this Amicus Brief already presented its answer to the question here at stake. Additionally it addressed why this rigor and simplicity causes no problem for economic stimulus provided by patent law in this extremely important area. The logical consequences of this rigor and simplicity namely are:

1) No, the human genome model is not patent-eligible, as this test shows that it is an abstract idea – already within the simple model world of biological chemistry (and the more if it were refined by a fundamental physics based model). Reasons are: It is impossible, for the human genome, to
    a. define the problem it has to solve – the bulk of them is unknown – and
    b. therefore define the respective simple independent concepts it, seen as a hypothetical solution, would use to this end, and
    c. therefore show that such hypothetical simple concepts are independent, and

d. therefore show that said concepts meet the step 2 requirement, as clarified below.

2) Yes, dependable patents as to all kinds of human genome based inventions may be granted, but only if their scopes are well-defined, i.e. they pass the above "non abstract idea" test, which implies that they define the problems they solve and the simple independent inventive/creative concepts they use to this end – elaborated on in Section IV.

III. COMPOUND CONCEPT DISAGGREGATION

The first step of the above test of the claimed invention at issue, its "compound inventive concept disaggregation" – induced by this court's *KSR*, *Bilski*, and in particular *Mayo* decisions2) – is indispensable for finding an unquestionable basis for precisely determining its scope of patent law protection.

Mathematics knows since centuries the need of an unquestionable basis for making precise statements: Here an "orthogonal coordinate system" usually serves as such a basis – often an "independent coordinates system" is sufficient. This court builds on this technique of Mathematics by its use of the term and notion "creative alias inventive concept", in its above decisions, when asking for precise descriptions of properties of claimed inventions: Its "creative/inventive concepts" of an invention determine its state space exactly as the Mathematics' "independent coordinates" of a system determine its state space (i.e. the space they both "span").

IT also builds on exactly this technique – since decades and even using the term/notion "concept" – for describing properties of new systems. There, this precisely definable notion of concept was developed, in the 1970s, for specifying data base systems, and since then elaborated on in its branches of Artificial Intelligence (AI), Natural Language (NL), Description Logic (DL), Knowledge Representation (KR), ... Today it is a fundamental notion in "advanced IT"[3].

Using this term/notion of "concept" in patent jurisdiction, i.e. in a NL environment, requires observing still another fundamental measure of caution, as discovered in the 1970s by David Parnas, one of the godfathers of SW-System-Design technique. Namely, the additional indispensable principle of "separation of concerns" in requirement statements in IT is the same as "disaggregation of compound inventive concepts" described in this Brief[3].

While compound concepts in natural languages are felt as being intuitive and hence are absolutely ubiquitous therein – e.g. in wordings of patent claims – they logically are extremely error prone (just as non-separated alias compound concerns are error prone in requirement statements in specifications of IT systems). By contrast, experience shows that independent inventive concept are next to trivial[3] – in particular if made "binary", also always trivially achievable[3] – and hence are logically error resistant. Finally, the separation of concerns requirement may exceed that of independence.

Most of the complicated discussions in patent precedents – in particular about testing a claimed invention as to the above quoted 4 §§ – are clearly due to the attempt to become precise about the relations of the meanings of these four sections to the meaning(s) of the invention's compound inventive concept(s), i.e. without first disaggregating it(them) into its(their) independent inventive concepts, also separating their concerns.

Yet it is known that in this way preciseness is often not achievable at all[2]!!! Even worse, accepting such compound inventive concepts in claim construction may result in the courts' decisions on them to be inconsistent and hence unpredictable. I.e.: These phenomena may be vastly avoided, in patent disputes, by admitting in its claim analysis solely simple (binary) independent disclosed inventive concepts – also if the claim's wording uses compound inventive concepts. There is absolutely no need to tolerate in patent precedents – even not when deciding on model based inventions such as human genome based inventions, as explained further down – dependent and/or "concerns not separating" concepts.

In its *Mayo* decision, the demands of this court clearly imply for the US patent precedents to insist in the just described state-of-the-art claims analysis that avoids such problems (clearly recognized in advanced IT).

So far this section explained the two quite different requirements, unquestioned in all advanced IT, to be met for enabling precise statements as to an invention, which imply the indispensable decomposition of compound inventive concepts into their simple independent inventive concepts. Putting it simply, these are,: The need of a dependable "coordinate system" for the predicates describing the invention's properties, and the need of assessing these properties represent separate and hence (usually) simple concerns involved in the inventive problem solution alias invention.

Without meeting these requirements, consistent arguing about model based inventions is impossible. But meeting them does not yet show that there is no need to leave the NL (though that of a person of pertinent ordinary skill) style of communications in model based patent precedents and to divert into the artificial thinking of the resp. model, in human genomes based inventions being the language of fundamental physics.

Disaggregating compound inventive concepts is nothing new in US patent precedents – but exactly what the *Mayo* decision asked for, and is consistent with the *KSR* and *Bilski* decisions as well as the recent CAFC decisions (also doing it implicitly)[3]. Yet, it should be understood as a clearly separate first step, being very significant for the claimed invention's test under the above 4 §§ 112, 102, 103, and 101. From the point of view of advanced IT, this first step is indispensable anyway.

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[3] "An Innovation Expert System, IES, and its PTR Data Structure, PTR-DS", Sections g.1-10 of footnote 4), on www.fstp-expert-system.com,

IV. THE DNA MODEL AND GRANTING PATENT PROTECTION TO HUMAN GENOME BASED INVENTIONS

This section first clarifies in **IV.1** the overall functionality that the mental DNA model of bio-chemistry represents of genetics, i.e. its process of cell division&diversification, and how it describes this functionality by means of "DNA concepts". **IV.2** explains in general terms, why this DNA model enables describing all genome based claimed inventions as required by the *Mayo* decision.

IV.1 Describing the Bio-Chemistry's Model of Genetics by DNA Concepts

This subsection shows how part of the commonly known model of the working of genetics with its all overarching DNA based bio-chemical process of cell division&diversification, the so-called DNA model, would be described by using the advanced IT notion of "concept". This DNA process describes the generation of compound DNA concepts of a developed genome out of elementary DNA concepts of its initial/undeveloped genome(s).

This description of the DNA model may focus, here, on its basic principles. This suffices already for precisely describing the kind and height of the creativity/ inventivity embodied by a human genome based invention over prior art, as needed for deciding whether this invention would pass its test under 35 U.S.C. §§ 112, 102, 103, and 101. The so focused description of the DNA model remains in this context (as set by the Sections I-III), comprising that it is plainly mental (i.e. totally abstracts from its vastly unknown physical fundaments) and may ignore also all other aspects of itself and of the invention, which are not related to these tests of it. Its description then is reducible to this context, too, i.e. to the following.

The DNA model's principle of a genome's cell division&diversification is the mirror image to the principle of an invention's compound inventive concepts disaggregation. In other words: The mental process of disaggregating all compound concepts of a genome developed by at least one step (i.e. the disaggregation of all of this genome's traits at this stage) into all their elementary concepts of this initial genome (i.e. of its genes) – called "fully decoding" this genome at this stage – is the inverse of the mental process of the bio-chemical DNA model, which describes this initial genome's cell division&diversification into this developed genome.

Here this mental bio-chemical process may be further reduced to its start/ stop relation between the (set of all by this process affected) genes of this initial genome to (the set of all affected) traits of this developed genome. Applying this reduction to the complete mental bio-chemical process of two just fertilized human genomes to a fully developed human being, it may be represented also as a relation between the set of all their genes and the set of all traits of this human being.

This abstract principle of the DNA model is clarified in some more notional detail, next, in other colloquial terms. The mathematical principle of its relation – in technical detail vastly unknown for the human genome – is known[3)III.2..Def3].

Anyone specific alias "individual" human genome and its genes exist in a resp. specific form alias instantiation. Genetics denotes any such form of a gene as an "allele" and of a genome's property "trait". IT terminology would denote genes, codons, genomes, phenotypes and their properties as "types" alias "classes", and their individual instantiations as "objects". Allele, trait, feature are object names, but genetics often calls objects just as types. Physical generations/interactions of objects are outside of the scope of this brief (and vastly unknown[I]).

In the description by means of concepts a particular use of the DNA model – e.g. for modelling particularities of a genome or therein of a process – the term "element" may denote any use specific said class or object, and any such "DNA concept" represents this element's property resp. a feature of it in this use. Hence, an element's DNA concept definition is simply given by the set of features of its property in this use of the DNA model – be the element therein e.g. a phenotype or a gene or an object of one of them, i.e. a trait resp. allele. This feature set of a DNA element may comprise its known as well as its novel features, i.e. of e.g. an allele its natural and its – by an invention – modified division/diversification capability.

These DNA model terms/notions enable specifying, by its use, any human genome based invention: Any such specification comprises a few traits (being compound DNA model concepts), a number of alleles (elementary DNA model concepts), and inventive nonDNA model concepts, together defining the invention.

IV.2 Describing a Human Genome Based Invention by Concepts

If a human genome based invention is created, which seeks protection by patent law, its inventive concepts got to be disclosed by its specification – up to the *Mayo* decision.

The above description of the DNA model shows that none of the DNA concepts is inventive in the sense of US patent precedents – any such concept describes a property (feature) of an element (object) that the DNA model assumes to exist in the nature, though it need not yet be known by bio-chemistry. .

Thus, such a human genome based invention got to be described by its inventive nonDNA concepts independent[2)III.2..Def2] of those of the DNA model, i.e. inventive properties (features) of this invention's non DNA element(s). Such inventive nonDNA concepts may describe, for this invention, e.g. the way in its genome (object) a gene or allele or codon or property or trait or ... is identified, or the minimal number of steps on this way, or these steps costs, or a side-effect of it/them on another element of the DNA model, or an impact on it/them by another such inventive nonDNA concept, or ..., but no fundamental physics statement. The mental DNA model sets no other limit as to defining such inventive nonDNA concepts' interactions with and/or impacts on DNA concepts – but it assumes that such interactions and/or impacts are, as usual, verified by bio-chemical experiments.

Thus a *Mayo* decision conforming description of a human genome based claimed invention then got to identify:

- At least one trait, being a modified compound concept definition of DNA phenotype object, thus reflecting the impact of an inventive/nonDNA concept on it, and at least one of the two following items:
- At least one allele, being a potentially modified concept definition of its DNA genotype object, thus potentially reflecting the impact of an inventive/nonDNA concept on it, and/or
- At least one relational object, being a potentially modified relational object of the above relation between features of said two concept definition sets, thus potentially reflecting the impact of an inventive/nonDNA concept on it.

That a notionally so structured description of a human genome based claimed invention actually solves the problem set out by the specification to be solved by it got to be confirmed by the person of pertinent ordinary skill based on experiments, as usual.

Finally note that performing this non abstract idea test has required the prior testing of said inventive concepts under § 112 as to their individual proper disclosures, under § 102 as to their novelty over a prior art, and under § 103 as to their nonobviousness over a combination of prior art teachings (more precisely: as to their not being anticipated by a combination of prior art teachings[2).III.1]). Those of these inventive concepts, which are "not drawn into a natural phenomenon" implied by their definitions by means of fundamental physics, are those for which the *Mayo* decision asked – as they provide the basis for indicating said claimed invention's patentability. To this end, these inventive concepts must also be tested for their independency. Dependent inventive concepts namely might disguise the factual obviousness of their claimed invention over prior art (what actually happened in patents granted for model based inventions, as explained in detail elsewhere2),III.2)).

CONCLUSION

A patent-eligibility test of a human genome based invention should start with assessing its scope is well-defined by applying the suggested non abstract idea test to it. The therein involved disaggregation of the invention's compound inventive concept(s) into independent inventive concepts should not refer to fundamental physics but only to the notions of the plainly mental DNA model.

Putting it more generally: For regaining clarity, predictability, and stability as to legal decisions on model based inventions and patents (to be) granted – not only but also as to human genes based ones – the sole unquestionable option seems to be to grant patent protection only to inventions of clearly defined scopes, as verified by their above "not abstract idea" test and refraining from using fundamental physics statements therein[4)].

Proceeding this way is consistent with 35 U.S.C.. Among the economically leading regions of the world, proceeding this way today is only possible under the US jurisdiction with its Supreme Court, its CAFC, and their substantial responsibilities under the US Constitution. It would take the US patent precedents to a level of development, which has been enabled by advanced IT, and which is capable of dealing with the model based inventions of the societally important branches of economy based on advanced sciences and technologies.

[4)] www.fstp-expert-system.com highly appreciates comments

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AMICUS
CURIAE
BRIEF

RECORD
AND
BRIEFS

Supreme Court U.S.
FILED
MAR 14 2013
OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

**On Writ of Certiorari to the United States
Court of Appeals for the Federal Circuit**

BRIEF FOR TARGET DISCOVERY, INC. AS *AMICUS CURIAE* IN SUPPORT OF AFFIRMANCE

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INTEREST OF *AMICUS CURIAE*

Target Discovery, Inc. is a diagnostics company that discovers, validates, and uses a new class of biomarkers (protein isoforms) to improve clinical diagnosis and management of disease.[1] Target Discovery's initial product focus is oncology with assays that better guide therapeutic choices and lower the overall costs of cancer treatment.[2] Target Discovery has numerous issued or allowed U.S. patents covering its unique platforms for protein isoform biomarker discovery, validation, and clinical application. All of these technologies are more broadly applicable for discovery biology and life sciences research. Two of these technologies have won industry recognition as seminal breakthroughs in their fields. Target Discovery believes that a strong patent system, including protection for biotechnology inventions, is essential for the development of new diagnostics and therapies.

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[1] In accordance with U.S. Supreme Court Rule 37.6, amicus curiae states that this brief was not authored, in whole or in part, by counsel for a party, and that no party made any monetary contribution to the preparation or submission of this brief other than the amicus curiae or its counsel. After reasonable investigation, Target Discovery, Inc. believes that (i) no member of its Board or Amicus Committee who voted to file this brief, or any attorney in the law firm or corporation of such a member, represents a party to this litigation, (ii) no representative of any party to this litigation participated in the authorship of this brief, and (iii) no one other than Target Discovery, Inc., or its members who authored this brief and their law firms or employers, made a monetary contribution to the preparation or submission of this brief.

[2] All of the parties have consented to filing of this amicus brief through their counsel. *See* U.S. Supreme Court Rule 37.3(a).

If the Court is to make major changes in the law, it should not do so based on erroneous facts, irrelevant legal arguments, or controversial policy theories. This case does not justify the radical change advocated by petitioners or the government.

SUMMARY OF ARGUMENT

The isolated DNA molecules claimed by Myriad are not "genes." What is actually claimed are chemical compositions that differ markedly in structure and function from genes as they exist in the human body. 44-45a, 51-53a, 56a ("[I]solated DNA is a tangible, man-made composition of matter defined and distinguished by its objectively discernible chemical structure."); MBr.44-45.[3] They are never produced in nature, but rather exist only when made by humans. Many of petitioners' arguments are irrelevant to whether these novel man-made chemical compounds are eligible for patents under § 101, but are instead based on erroneous scientific and legal assumptions and on controversial policy arguments. Surprisingly, the government's brief also contains errors of law and fact, possibly due to the absence from the brief of the U.S. Patent and Trademark Office ("PTO"), the agency with scientific and patent law expertise.

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[3] Abbreviations: MBr. is Brief for Respondents, PBr. is Brief for Petitioners; GBr is Brief for the United States as Amicus Curiae in Support of Neither Party; JA is Joint Appendix; numbers followed by "a" are pages of Petitioners' Appendix.

Petitioners' proposal that isolated DNA molecules are not eligible for patenting under § 101 would upset settled expectations and invalidate thousands of patents, sending an entire segment of the U.S. economy into uncertainty. 61-62a; 86-89a (Moore, J., concurring); MBr.14-15, 33, 38-39; GBr.29-30. Whether these useful, novel, man-made molecules that never existed in nature are eligible for patenting under § 101 should be decided based on the facts about what is actually claimed, and not on disputed controversial policy arguments.

The government's implication that *all* molecules isolated from biological sources (and not just isolated DNA molecules) are unpatentable under § 101 because they are "products of nature" would overturn the practice of over 100 years. Patenting of isolated chemicals from natural sources has brought enormous benefits by making available valuable compounds that were not before accessible to the public. Elimination of these patents would have a drastic effect on the biotechnology, pharmaceutical, and numerous other industries.

Courts have occasionally mentioned a "products of nature" exception to patent eligibility in dicta, without analyzing it in depth. This case illustrates the difficulty of going beyond simple hypothetical examples to deal with modern technology. A better course would be to view *all* compositions of matter as patent eligible, as stated in the statute: "Whoever invents or discovers *any* new and useful . . . composition of matter . . . may obtain a patent therefor, *subject to the conditions and requirements of this title*." 35 U.S.C. § 101 (emphases added). Thus, while leaves plucked from trees and kidneys removed from bodies would be patent *eligible* because they are compositions of matter, they would clearly *not be patentable* because they would not satisfy the other "conditions and requirements of this title," namely, the requirements for novelty and nonobviousness." Interpreting the statutory language in this way would also be consistent with the 100-year old practice of granting patents to certain compositions isolated from natural sources, thus making those compositions and their benefits accessible to the public.

Evidence suggests that the Myriad patents have not inhibited research on the *BRCA* genes and are not an impediment to developing methods of whole gene sequencing. If needed, Congress is the appropriate forum and can pass focused legislation to remedy actual problems. Patents, including patents to isolated DNA molecules and other biological molecules, can provide incentives for the development of diagnostics and treatments for cancer and other diseases.

ARGUMENT

I. Petitioners and Government Mix Erroneous Scientific and Legal Arguments

A. Petitioners Misinterpret the Claims

As an initial matter, petitioners' arguments ignore the basic rules of claim construction. This Court has long recognized that "[u]nder the statute, it is the claims of the patent which define the invention." *Altoona Publix Theatres v. Am. Tri-Ergon Corp.*, 294 U.S. 477, 487 (1935). The validity of each claim must be evaluated independently. *Id.* Furthermore, disclosure in the specification cannot be imported into the claims. *R.R. Co. v. Mellon*, 104 U.S. 112, 118 (1881)("[T]he scope of letters-patent should be limited to the invention covered by the claim, and that though the claim may be illustrated, it cannot be enlarged by the language used in other parts of the specification."); *Cont'l Paper Bag Co. v. E. Paper Bag Co.*, 210 U.S. 405, 419 (1908)("[T]he claims measure the invention. They may be explained and illustrated by the description. They cannot be enlarged by it.").

Some of petitioners' arguments ignore these cardinal rules. For example, they assert that "none of the claims is limited to cDNA." P.Br.23. Yet claim 2 of U.S. Patent No. 5,747,282 ("the '282 patent") unambiguously claims a cDNA.[4] JA779 ("MOLECULE TYPE: cDNA"). This error is relevant because the government and all three Federal Circuit judges held that cDNA molecules are eligible for patenting. Petitioners explain that "[b]ecause the patents define the term 'DNA' used in this claim identically to claim 1 to include all versions of the nucleotide sequence (and more), the sequence referenced is solely illustrative." PBr.14. This impermissibly reads terms from the specification into the claim. The claim is not "solely illustrative."

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[4] Claim 2 of the '282 patent reads: "The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1." JA822.

It precisely defines one specific DNA molecule, a cDNA molecule.

Petitioners also import language from the specification into the claims when they argue that the claims encompass RNA and DNA chemically modified by methylation. PBr.30-31. These elements are absent from the claims. The broad definitions in the patents (JA754-55) are speculations about all the embodiments that Myriad hoped to patent. Indeed, subject matter described in the specification but not claimed is dedicated to the public. *See Miller v. Brass Co.*, 104 U.S. 350, 352 (1881); *McClain v. Ortmayer*, 141 U.S. 419, 423-24 (1891).

B. Human Genes Are Fundamentally Different Than the Claimed Isolated DNA Molecules

Petitioners use the terms "genes" and "isolated DNA" interchangeably. *E.g.*, PBr.9, 19, 44. Using the terms interchangeably confuses the most basic assumption at issue—whether the challenged claims are in fact human genes. The patented claims are directed to isolated DNA sequences that are structurally and functionally distinguishable from their native gene counterparts. The isolated DNA molecules in dispute are not human genes as they exist in the body, and they are more than mere segments of DNA as petitioners contend. *See* PBr.4 n.1. Rather, they are man-made chemical compounds that do not exist in nature. 44-45a, 50-55a. The terms are, therefore, not interchangeable.

According to the government, cDNA[5] claims are patent eligible, whereas the other isolated DNA claims are ineligible because they are allegedly "isolated but otherwise unmodified human DNA." GBr.9. The government thus reasons that the physical changes that occur when isolating human genomic DNA "do not significantly alter the structure or function of the relevant DNA segments." *Id.*

The government implies that the only structural difference between isolated DNA and native DNA is the isolated DNA's "snipped" ends. *Id.* As set forth below, the isolated gene is not simply "snipped" out of its *in vivo* chromosomal context. The government fails to acknowledge that the process required to isolate the *BRCA* genes from the native cellular environment significantly alters the chemical structure, size, and function of the molecules.

---

[5] Molecules of cDNA, as the government correctly observes, are "synthesized nucleotide sequences that contain only the exons of a naturally occurring gene." GBr.18. These "artificial DNA molecules" are patent-eligible inventions requiring "significant manipulation and alteration of naturally occurring genetic materials." *Id.* But the chemically isolated DNA macromolecules and fragments are patent eligible for the same reasons.

1. Isolated DNA Molecules Are Structurally and Functionally Distinct from Genes

Isolating a DNA sequence from its native environment does not produce a product that is structurally identical to the precursor but for its lack of association with cellular components. Isolating DNA chemically manipulates it to yield a markedly different structure than its native counterpart. 52a. For instance, the isolated DNA sequence is no longer covalently bonded to adjacent nucleotides in the chromosome. 51a. Breaking the covalent bonds, as is done as a first step in isolating the genomic DNA sequence, converts the genomic DNA molecule into a different chemical entity. The new molecule formed by breaking covalent bonds is structurally and chemically different than the original molecule. It no longer contains at least two phosphodiester bonds, and contains a hydrogen (H) atom and hydroxyl (-OH) group that were not present when it was in its native molecule.

Petitioners would like the Court to discount these basic structural and chemical differences because the native and isolated molecules both function to provide "information content" needed to make a protein. PBr.9. They contend that the isolated DNA molecules' loss of covalent bonds is insufficient to render the molecule markedly different. Judge Lourie, who holds a doctorate in chemistry, found the covalent bonds, which are the "defining boundary between one molecule and another," to be particularly important in distinguishing isolated DNA as a different chemical molecule from chromosomal DNA. 54-55a.

Petitioners err for two reasons. First, they focus on a single difference between the isolated molecule and the genomic, native DNA instead of acknowledging all of the other differences. 55a. Second, the physiological use or benefit of an isolated DNA sequence, while perhaps relevant to method claims, is *not* relevant to the patent eligibility of *compositions of matter* claims. *Id.* Chemical compositions are claimed by their structure and not by their use.

As it is undisputed that a gene is a "material[] having a chemical nature," *id.*, the proper lens through which to assess patent eligibility under 35 U.S.C. § 101 is a structural analysis. Here, comparing the structure of the isolated DNA molecule to the structure of genomic DNA shows significant differences—at the least, in the lack of two phosphodiester bonds linking nucleotides to one another. There are other structural differences, such as the loss of epigenetic modifications in the isolated molecules. Fragments of DNA such as probes and primers have enormous differences in size compared to a gene. 51a. Thus, isolated DNA molecules are structurally markedly different from their native genomic counterparts.

2. The Process Used to Isolate Genomic DNA Results in a Markedly Different Compound Than That Which Is Found in Nature

Additionally, physically extracting chromosomal DNA from a cell is only the first of many steps in creating the claimed isolated sequences. Once removed from the cell, the extracted chromosomal DNA is used by scientists to create "genomic libraries" or to mechanically amplify the sample to extract the isolated sequence of interest. To create the initial genomic DNA library, scientists cleave the chromosomal DNA into short fragments. The fragments are individually inserted into "vectors" (vehicles used to transfer DNA sequences to a target cell), which are transformed into cells that are grown in culture in the laboratory. As the cells multiply and proliferate, the DNA fragment replicates so that the grown culture contains multiple copies of the DNA fragment. The engineered collection of cells is thus termed a "genomic DNA library," where the short stretches of DNA in the vectors have been produced synthetically via replication. The final step in the isolation process is screening the library and selecting a clone that contains a vector having a sequence of interest. If the DNA sequence of the gene of interest has already been determined, scientists can use more convenient mechanisms, such as polymerase chain reaction (PCR) amplification,[6] to mechanically synthesize a large number of copies of the molecule of interest. *See* Harvey Lodish et al., Molecular Cell Biology 231-33 (3d ed. 1995); JA749, 7:53-8:4 (describing how *BRCA1* gene was isolated from yeast and bacteria artificial chromosome (YAC and BAC) vectors).

Understanding the process by which genomic DNA is isolated shows that DNA molecules are not just "snipped" loose from a three-dimensional linear stretch of chromosomal DNA, GBr.22, but rather are made by scientists as fragments in the laboratory. Both the creation of genomic libraries and the amplification of a target DNA sequence convert what was a highly structurally complex chromosome into a stretch of DNA lacking structural complexity.

Epigenetic modifications, which "alter the activities and abilities of a cell without directly affecting and mutating the sequence of the DNA" also distinguishes the structure and function of isolated DNA from that of the native molecule. *See* Anders H. Lund & Maarten van Lohuizen, *Epigenetics and Cancer*, 18 Genes & Dev. 2315, 2315 (2004)("Lund"). Examples of epigenetic modification include DNA methylation, histone modification, and noncoding RNAs. *Id.* at 2315–35. Gene expression that is controlled by epigenetic modification changes over time and differs from cell to cell within an individual as well as between individuals. Rudolf Jaenisch & Adrian Bird, *Epigentic Regulation of Gene Expression: How the Genome Integrates Intrinsic and Environmental Signals*, 33 Nature Gen. Supp. 245, 250-51 (2003). One common type of epigenetic modification, DNA methylation, results in the modification of cytosine residues in the nucleic acid sequence. Lund at 2315–20. DNA methylation is tightly connected to cancer development, and indeed, *BRCA1* hypermethylation has been observed in breast cancer tumors. *Id.* at 2320; Valgerdur Birgisdottir et al., *Epigenetic Silencing and Deletion of the BRCA1 Gene in Sporadic Breast Cancer*, 8 Breast Cancer Res. 1, 8 (2006), http://breast-cancer-research.com/content/pdf/bcr1522.pdf. Epigenetic modifications of chromosomal DNA are lost when genes are isolated,[7] and as such, genomic DNA in its native environment is structurally and functionally different than isolated genetic sequences.

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[6] PCR (polymerase chain reaction) amplification is a laboratory technique where a single copy of double-stranded DNA can be used as a template to create a large number of copies of a target sequence. *See* PCR, http://www.ncbi.nlm.nih.gov/projects/genome/probe/doc/TechPCR.shtml (last visited March 14, 2013); JA352-53.

Petitioners argue that genomic DNA and its isolated counterparts are not "markedly different" in structure or function by suggesting that when isolated DNA is reinserted into the cell, it maintains its previous function. PBr.9, 35. In support, petitioners cite to two "classic experiments" performed 65 and 27 years ago. *Id.* at 35. These experiments, conducted in *Streptococcus Pneumonia* bacteria and mouse fibroblast cells, illustrated that DNA is responsible for passing heritable traits from one generation to the next. JA649–53. It is overreaching, however, to suggest that these experiments show that if isolated human DNA sequences, such as those encoding *BRCA1*, could somehow be reinserted into the genome they would maintain their same function. Indeed, although the *theory* of human gene therapy has been around for decades, problems associated with transient gene expression, unpredictable gene insertion sites, and vector toxicity have rendered the promise of this technique largely unrealized. *See* Matthew Porteus et al., *A Look to Future Directions in Gene Therapy Research for Monogenic Diseases*, 2 PLoS Genet., 1285, 1285 (2006), *available at* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1584267/; *Gene Therapy*, Human Genome Project Information, http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetherapy.shtml (last modified Aug. 24, 2011). In short, for unknown reasons the reinserted DNA does not function in the same manner as the chromosomal gene it was meant to replace.

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[7] Although DNA methylation results in a methyl group covalently bonded to a cytosine and thus would be present in the initial chromosomally extracted DNA, *see* JA644–45, the methylation is lost during the PCR amplification necessary to create synthetic copies of the isolated gene. Yingying Zhang & Albert Jeltsch, *The Application of Next Generation Sequencing in DNA Methylation Analysis*, 1 Genes 85, 87 (2010).

C. Simple Hypothetical Analogies Fail to Adequately Exemplify the Isolated DNA Molecules

Various hypothetical analogies to isolated DNA molecules appear in the briefs and in the Federal Circuit's opinion. PBr.2, 34, 56-57; GBr.22, 24-25; 59-61a; 102-04a, 107-08a, 109a n.4 (Bryson, J., dissenting); 84a (Moore, J., concurring). These analogies are oversimplified and lack the nuances that demonstrate the "intervention of man that created a new molecule." 82a n.3 (Moore, J., concurring); *Diamond v. Chakrabarty*, 447 U.S. 303, 313 (1980). They are also not supported by science. *Cf.* Section I.A-B, *supra.* Isolated DNA molecules are not simply removed from their natural environment; the chemical structure of the isolated DNA molecules is not the same as those found in native DNA. These "analogous" separations miss this key feature of patent eligibility for isolated DNA molecules, namely that "isolating" DNA results in a new chemical entity!

These hypothetical examples compare isolated DNA molecules to removing things from their natural environment, such as removing a kidney from a body, snapping a leaf or limb from a tree, or plucking a plant from the ground.[8] PBr.2, 34;

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[8] Petitioners label the bacterial strains in *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948), as "isolated." PBr.32. While the bacteria were removed from their natural environment, PBr.32-33, they were not isolated analogously to isolated DNA molecules. Nor were they chemically altered like

MBr.55-56; GBr.22-24; 59-61a; 107-08a (Bryson, J., dissenting). Given the man-made nature of isolated DNA and its significant differences from molecules in nature, the better comparison would be, for example, using dissociated kidney or embryonic stem cells, or stem cells from the apical meristem of a plant, to grow *in vitro* isolated parts of the kidney (such as the glomeruli) or guard cells forming the stomata, respectively, that are never found alone in nature. No one familiar with kidney physiology or the components of a leaf would consider the resulting individual parts of the kidney or leaf to be equivalent to the whole.

Analogies comparing isolated DNA to things merely "carved out" or separated with no chemical transformation are flawed. The patentability of a "baseball bat" or "marble slab" is not analogous to isolated DNA. 108a, 109a n.4 (Bryson, J., dissenting); MBr.40-41; 84a & n.4 (Moore, J., concurring). The analogy of panning for gold is fatally simplistic as well. PBr.2, 34; MBr.55-56. While removing gold from a riverbed "isolates" the nugget from its surroundings, the nugget does not transform. And like the gold nugget, cleaning dirt off of a diamond, 104a (Bryson, J., dissenting), does not chemically transform that diamond into a human-made invention

Similarly, comparing isolated DNA to "coal beneath the earth, cotton fibers mixed with cotton

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the bacteria in *Diamond v. Chakrabarty*, 447 U.S. at 305, (or the isolated DNA molecules in this case). *Funk Bros.*, 333 U.S. at 129-30.

seeds, the stigmas of the saffron flower . . . . lithium, boron and barium" is flawed. GBr.24; *see also* 102-04a (Bryson, J., dissenting). Although these natural things are all physically separated to be "useful," they are not chemically transformed into different molecular entities. Isolating DNA molecules, however, does transform genomic DNA into a different molecular entity. The reason why all of these simple examples seem to be clearly unpatentable is not because they are "products of nature." It is because they are facially unpatentable under other provisions of the patent statute.

D. Petitioners Improperly Conflate § 101 Patent Eligibility with the Requirements for Patentability

As the Federal Circuit summarized, "[t]he issue is patent eligibility, not patentability." 43a, 44a ("[O]ther general questions relating to patentability and use of patents are issues not before us."), 62a, 70a. There is a distinct difference between subject matter eligibility, novelty, obviousness, written description, and enablement. For example, this Court stated that novelty "is of no relevance in determining whether the subject matter of a claim falls within the § 101 categories of possibly patentable subject matter." *Diamond v. Diehr*, 450 U.S. 175, 188-90 (1981); *see also Classen Immunotherapies, Inc. v. Biogen IDEC*, 659 F.3d 1057, 1075 (Fed. Cir. 2011), *cert. denied*, 133 S. Ct. 973 (2013)(Rader, C.J., additional views)(noting that "[m]any litigation-spawned applications of section

101" improperly focus on "a question of patentability depending on prior art and adequate disclosure"). The substantive *requirements* for patentability under §§ 102, 103, and 112 apply only to inventions that have passed the antecedent question of § 101 patent *eligibility*. *See Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010).

The Federal Circuit explained that certain Supreme Court decisions are based on a "lack of novelty, not patent-eligible subject matter," 48a n.10, identifying *American Wood-Paper Co. v. Fibre Disintegrating Co.*, 90 U.S. 566, 596 (1874), and *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 311 (1884). Petitioners rely on these cases in arguing the patent ineligibility of Myriad's claims. PBr.39, 51-52.

Petitioners, and in certain instances the government, continue to conflate novelty with subject-matter eligibility. They argue that the claims are ineligible for patentability because Myriad "did not invent" the subject matter of the claims. PBr.37-39 (discussing "inventive concept"). In so doing, however, they rely on cases concerning novelty, where the claims covered prior art compositions of matter.[9]

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[9] Reliance on early case law highlights the nuances between § 101 and the conditions for patentability, in part because separate standards for assessing patents did not exist until the 1952 Patent Act. *See generally* MBr.23-25 (describing *Funk Bros.*, 333 U.S. 127, as an obviousness—not § 101—case); *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 14-15 (1966)(describing the 1952 Act).

For example, certain pre-1952 cases were cited where claims for "substantially pure tungsten having ductility and high tensile strength," and for ductile vanadium were respectively found invalid and not allowed. PBr.38-39; GBr.25. The purified metals existed in the art and the claims covered only natural and inherent characteristics of those known metals. *See Gen. Elec. Co. v. De Forest Radio Co.*, 28 F.2d 641, 642-43 (3d Cir. 1928); *In re Marden*, 47 F.2d 958, 958-59 (C.C.P.A. 1931)("Vanadium . . . has been known to exist by metallurgists for more than a century."). Those cases rested not on lack of patent eligibility but rather on the lack of novelty of the claimed subject matter assessed against the prior art.[10] Similarly, in *In re Merz*, 97 F.2d 599, 600-01 (C.C.P.A. 1938), the compound ultramarine was well known in the prior art, which rendered "artificial ultramarine" unpatentable. PBr.39. Petitioners also rely on *Ex parte Latimer*, 1889 Dec. Comm'r Pat. 123, 126, where a claim to fibers extracted from pine needles was rejected because "[t]here is no chemical combination . . .by which the fiber becomes something new or different from the fiber in its natural state." In that case too, the claimed characteristics were known in the art and lacked any new or useful property. *Id.*

Not only do petitioners conflate inventive concept and novelty, but they also maintain improper arguments about the breadth and scope of the claims' reach under § 101—arguments properly reserved for a § 112 or claim construction analysis. *See* 60a; PBr.31, 40. In arguing that Myriad's claims are not patent eligible, petitioners proffer preemption arguments resembling enablement arguments. They argue that "[a]ll of the claims reach all uses of the genes in DNA, cDNA, or RNA form and all variants and fragments of the genes, including future uses not yet identified or technically achievable." PBr.41. But they cite *O'Reilly v. Morse*, 56 U.S. 62 (1853), a case concerning § 112 written description. *Morse* explains that a patentee "can lawfully claim only what he has invented and described, and if he claims more his patent is void." *Id.* at 121; *see Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1359 (Fed. Cir. 2010)(Newman, J., additional views)(citing *Morse* as concerning adequate disclosure under § 112).

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[10] *See also* Kevin Noonan. *An Antidote to the Politics of the Human Gene Patenting Debate*, SCOTUSBlog (Feb. 6, 2013) http://www.scotusblog.com/2013/02/an-antidote-to-the-politics-of-the-human-gene-patenting-debate.

In relying on cases that do not distinguish between patent eligibility and patentability, petitioners confuse § 101 with other legal theories that have not been asserted and are not at issue in this case.[11]

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[11] Petitioners also rely on *American Fruit Growers v. Brogdex Co.*, 283 U.S. 1 (1931), asserting that this Court rejected the patenting of an orange coated with borax. PBr.29 (citing *id.* at 11-12). But the issue in that case was whether the borax-coated oranges fit within one category of patent eligible subject matter, an article of manufacture, and not whether they were "products of nature." There, the process claims were reversed as anticipated by an earlier patent. *Am. Fruit Growers*, 283 U.S. at 11-14; *see also* GBr.20 n.6 (citing *Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985)(rejecting claims as anticipated under § 102)).

II. A Better Approach: Consider All Compositions of Matter Eligible for Patenting, and Apply the Statutory Requirements of Patentability

This case illustrates the great difficulty of applying a "products of nature" standard to the eligibility for patenting of compositions of matter. The uncertainty is illustrated by the different conclusions reached by the parties and judges, by the tendency to conflate patent eligibility and patentability, and by the inadequacy of simple examples. As Justice Frankfurter wisely observed: "It only confuses the issue, however, to introduce such terms as 'the work of nature' and the 'laws of nature.' For these are vague and malleable terms infected with too much ambiguity and equivocation." *Funk Bros.*, 333 U.S. at 134-35 (concurring).

A better course would be to view *all* compositions of matter as eligible for patenting. This is consistent with the language of the statute: "Whoever invents or discovers *any* new and useful . . . composition of matter . . . may obtain a patent therefor, *subject to the conditions and requirements of this title*." 35 U.S.C. § 101 (emphases added). The narrow judicial exceptions to patent eligibility (laws of nature, abstract ideas, natural phenomena) do not fall in the patent eligible categories of § 101, but compositions of matter do.

Although they are compositions of matter, the simplest hypothetical examples discussed in the briefs (leaf from a tree, kidney removed from the body, etc.) would undoubtedly be unpatentable as clearly lacking novelty and as obvious (35 U.S.C. §§ 102 and 103). A plant in the forest, gold in a stream, and electrons would all be anticipated under 35 U.S.C. § 102 based on their prior existence. While modestly modified by man, a leaf snapped from a tree or a kidney removed from the body would be anticipated and also invalid as obvious under 35 U.S.C. § 103.[12] Isolated DNA molecules should be patent eligible since they are compositions of matter and they do not fall within the three patent-ineligible exceptions—laws of nature, abstract ideas, natural phenomena. The patent law, however, would prohibit a claim to an isolated DNA molecule that was not novel, was obvious, or lacked sufficient support. Thus, there is no reason to fear improper patents preempting compositions of matter in the public domain. Instead, patents on compositions of matter would receive a sophisticated analysis of validity in the PTO and courts, instead of an uncertain and somewhat subjective "product of nature" rejection.

This analysis would also rationalize the 100-year old practice of granting patents to certain compositions isolated from natural sources, thus making those compositions and their benefits accessible to the public. Patenting of those molecules can be evaluated with the same approach as the well-developed patent law regarding inherency. "The fact that a version of the invention may have previously existed, unrecognized, unavailable, and unappreciated, should be irrelevant to patentability under either novelty or subject matter. The proper question is: did the inventor make available to humankind something we didn't have available before?" Dan L. Burk, *Anticipating Patentable Subject Matter*, 65 Stan. L. Rev. 109, 114 (2013); Dan L. Burk & Mark A. Lemley, *Inherency*, 47 Wm. & Mary L. Rev. 371 (2005).

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[12] One requirement of § 101 does impact validity as opposed to patent eligibility, the requirement of utility. *Brenner v. Manson*, 383 U.S. 519, 530-36 (1966). Among other things, many isolated DNA molecules would be unpatentable for lack of a known use. 2001 PTO Utility Examination Guidelines, 66 Fed. Reg. 1092, 1095 (Jan. 5, 2001).

III. Patent Eligibility Should Not Be Decided on Controversial Theories About Potential Effects of Myriad's Claims

A. Contrary to Petitioners' Assertions, the Claims in Myriad's Patents Do Not Preempt Use of the *BRCA* Genes

The Myriad patents do not preempt research using the *BRCA* genes. Any potential preemption is limited as the seven challenged patents expire prior to December 19, 2015. 58a. The Federal Circuit correctly recognized that any preemption is "very limited in the case of the present patents" and that "a limited preemption is inherent in every patent" by virtue of the right to exclude. 58-59a; *see also* GBr.17 ("This inquiry into preemptive effect is not an exclusive test of the patent-eligibility of a product."); MBr.46 ("'[P]reemption' is not a test for patent-eligibility.").

Petitioners allege that Myriad's patents foreclose any opportunity for researchers to use the native *BRCA* genomic sequence, preventing and deterring research. PBr.3, 43. The *BRCA* genes are only covered broadly because of Myriad's numerous claims in its portfolio. To properly assess this allegation and determine if the claims are invalid, Myriad's patent claims must be analyzed on a claim-by-claim basis. *See Altoona*, 294 U.S. at 487 ("[I]t is the claims of the patent which define the invention. . . . And each claim must stand or fall, as itself sufficiently defining invention, independently of the others."). However, without the benefit of claim construction and a claim-by-claim analysis for invalidity, petitioners' allegation cannot be resolved.

Despite the lack of claim construction in this matter, it is possible to observe that Myriad's patents do not prevent researchers from using *BRCA* genes. Since 2000, over 8,000 articles have been published reciting *BRCA1*,[13] with a spike in the publications occurring in 2012.[14] This large volume of work reflects researchers' perception that the *BRCA1* gene is accessible for research. This perception is shared not only by university researchers, but also by representatives of biotechnology and pharmaceutical firms.[15] *See* John P. Walsh, *Effects of Research Tool Patents and Licensing on Biomedical Innovation*, in Patents in the Knowledge-Based Economy 285, 287 (Wesley M. Cohen & Stephen A. Merrill, eds., 2003)("Walsh").

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[13] Results from the search run in PubMed for "BRCA1" on March 10, 2013. NCBI PubMed. http://www.ncbi.nlm.nih.gov/pubmed (last visited March 10, 2013).

[14] Nearly all of the challenged Myriad patents issued during 1997 or 1998 except for U.S. Patent No. 6,033,857, which issued in May of 2000. Excluding the years 1998 and 1999 from the search, a PubMed search returned 8057 articles. Including 1998 and 1999, the PubMed search returned 8804 articles. 2012 has the highest number of articles regarding *BRCA1*, with 869 articles available on PubMed.

Researchers were once concerned that a patent to an isolated DNA molecule would grant rights to the whole native gene or encoded protein on the patent owner, which would block access to these genomic research tools. *Id.* at 299. Both in theory and in practice, however, researchers now appreciate that isolated DNA molecule patents grant only limited rights to isolated DNA molecules; limited to the exact isolated DNA sequence that is claimed. *Id.* Likewise, biotechnology and pharmaceutical firms have not become lost in the patent thicket of isolated DNA molecule patents. [16] *Id.* at 298; *see generally* Timothy Caulfield et al., *Evidence and Anecdotes: An Analysis of Human Gene Patenting Controversies*, 24 Nat. Biotechnol. 1091, 1091-93 (2006). In fact, a survey reported that many patent-holding firms embrace university researchers working on the patented invention so long as the work is non-commercial. Walsh at 317. University researchers benefit the patent owners by exploring the patented invention to develop increased understanding of the invention. *Id.* Even on the reportedly rare occasion that a patent owner sends a cease and desist letter to a university, the university appears to remain unencumbered by the threat. *Id.* at 317-18.

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[15] The cited study reports the results of interviews with 70 individuals "at biotechnology and pharmaceutical firms and universities in considering the effects of research tool patents on industrial or academic biomedical research." Walsh at 287.

[16] *See id.* at 298 ("One biotechnology executive stated: 'I am hard pressed to think of a piece of research that we haven't done because of blocked access to a research tool.'").

For at least the wide-spread use of *BRCA1* in research reflected in the understanding of the scientific community, the Court should not hold that Myriad's patents preempt the native DNA of the claimed isolated DNA molecules. The Court should not decide this controversial issue of gene patent validity on nearly expired and unconventional patents.

B. The Broad Claims in the Myriad Patents Are Not Representative of Modern Claims to Isolated Genomic Molecules

In the late 1990s when applications for the Myriad patents were filed, the study of the human genome was still developing as a new area of technology. In 2003, the Human Genome Project completed its goal of identifying all genes in human genomic DNA, and it was not until this accomplishment that the scientific community appreciated the volume of redundancy in the human genome. John Aach et al., *Computational Comparison of Two Draft Sequences of the Human Genome*, 409 Nature 856, 856 (2001). Accordingly, and in light of this lack of appreciation, claims to isolated DNA molecules filed before 2003 are likely overbroad.

After 2003 and the publication of the human genome sequence, researchers could draft their claims in light of the redundancies in the genetic code to more succinctly describe the invention. Instead of drafting claims to isolated DNA molecules themselves, patents frequently claim only cDNA.[17] Christopher M. Holman, *Will Gene Patents Derail the Next Generation of Genetic Technologies?: A Reassessment of the Evidence Suggests Not*, 80 UMKC L. Rev. 563, 595 (2012)("Holman I"). The PTO became more experienced with examining claims to isolated DNA molecules because the human genome sequence was available as prior art. Lori Pressman, *DNA Patent Licensing Under Two Policy Frameworks: Implications for Patient Access to Clinical Diagnostic Genomic Tests and Licensing Practice in the Not-for-Profit Sector*, 6 Life Sci. L. & Industry Rep. (BNA) No. 6, at 329, 331 (Mar. 23, 2012). This ultimately led to the PTO issuing better claims to isolated DNA molecules.[18] Indeed, a study observes that DNA sequences available in GenBank prior to the filing date of Myriad's patents might anticipate or render the claims obvious. Thomas B. Kepler, *Metastasizing Patent Claims on* BRCA1, 95 Genomics 312, 314 (2010). A broad reading of the claims might also implicate invalidity under 35 U.S.C. § 112. Holman I at 581.

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[17] *See* Holman I, at 595 ("Most of these patents appear to have been filed based on the discovery of a protein-encoded cDNA, and with the intent of protecting the use of the cDNA in the recombinant production of the encoded protein, not as a subject of genetic testing.").

[18] "The announcement of a working draft of the human genome in 2001, and the completed sequence in 2003, is particularity critical in the context of WGS [whole genome sequence], because it strongly suggests that any patent filed since then cannot be both valid and infringed by WGS, at least by the conventional methodologies used in the initial sequencing of the human genome." Christopher M. Holman, *Debunking the Myth that Whole-Genome Sequencing Infringes Thousands of Gene Patents*, 30 Nature Biotechnol. 240, 242 (2012).

C. Claims to Isolated DNA Molecules Do Not Preempt Genomic Sequencing

Patents to isolated DNA molecules do not prevent researchers from sequencing the human genome. For a method of DNA sequencing to infringe a claim to isolated DNA molecules, the method must use or make the isolated DNA molecule exactly as claimed. Christopher M. Holman, *Debunking the Myth that Whole-Genome Sequencing Infringes Thousands of Gene Patents*, 30 Nature Biotechnol. 240, 240 (2012)("Holman II"). Any partial sequences that contain some of the same nucleotide sequence as the isolated DNA molecule cannot infringe claims requiring a larger sequence. The traditional methods of sequencing a gene do not infringe the isolated DNA molecule patents. Using either traditional methods of sequencing or newer genome sequencing technologies, a claim to isolated DNA molecules will rarely be infringed. PBr.7, 41-45; Holman II at 242-43.

Unlike the traditional methods of DNA sequencing, the next generation of genomic sequencing is unlikely to infringe isolated DNA molecule claims. These new sequencing technologies are faster and more likely to be used in the context of personalized medicine than traditional sequencing methods. *See* W. Nicholson Price, II, *Unblocked Future: Why Gene Patents Won't Hinder Whole Genome Sequencing and Personalized Medicine*, 33 Cardozo L. Rev. 1601, 1606, 1624 (2012)("Price"); Holman I at 579-80. *See generally* Jonas Korlach et al., *Real-Time DNA Sequencing from Single Polymerase Molecules*, 472 Methods Enzymol. 431 (2010). Thus the Myriad claims do not prevent research of the whole genome or even the *BRCA* genes.

IV. Other Molecules from Biological Sources Should Not Be Unpatentable as "Products of Nature"

A. Isolated Biological Molecules Are Patentable

Isolated molecules from natural sources require human intervention even when the molecules are not changed chemically. The utility of the isolated or purified molecules can differ substantially from the molecules in nature. The patenting of isolated or purified molecules has been accepted for 100 years, and has contributed to the progress of medicine, biotechnology, and other fields. Patenting has not deprived the public of the use of those molecules, but instead has provided the commercial incentive to discover and make them available.

Patenting molecules from natural sources has a long history. 52-53a. In a leading case, *Parke-Davis & Co. v. H.K. Mulford Co.*, Judge Learned

Hand found that purification of adrenaline resulted in the same molecule that existed in the body, but the purified adrenaline was "for every practical purpose a new thing commercially and therapeutically." 189 F. 95, 103 (S.D.N.Y. 1911); *see also Merck & Co. v. Olin Mathieson Chem. Corp.*, 253 F.2d 156, 161-64 (4th Cir. 1958)(purified composition of vitamin B-12 was patentable because the purification process resulted in a product that was therapeutically effective, whereas the natural form was not).

Prostaglandins, compounds important in major disease processes, are present in the body only in minute quantities. The patenting of pure prostaglandins, *In re Bergstrom*, 427 F.2d 1394, 1394 (C.C.P.A. 1970), made them available to researchers leading to progress in the understanding and treatment of many diseases, such as rheumatoid arthritis. *See, e.g.*, Sune Bergdtrom, Nobel Prize Lecture: The Prostaglandins: From the Laboratory to the Clinic (Dec. 8, 1982), *available at*: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1982/bergstrom-lecture.pdf. Similarly, purified vitamin B-12, a natural product, was held to be patentable. *Merck*, 253 F.2d at 156. The court explained that purified vitamin B-12 was "far from the premise of the [naturally occurring] principle. . . . The new product, not just the method, had such advantageous characteristics as to replace the [naturally occurring] liver products. What was produced was, in no sense, an old product." *Id.* at 162-63; 77a.

Isolation gave these biological compounds important new uses. These were not "part of the storehouse of knowledge of all men . . . free to all men." *Funk Bros.*, 333 U.S. at 130. No one had access to these valuable molecules until the inventors' ingenuity provided them. If a molecule never existed in nature in a pure or isolated form, then the pure molecule is "nonnaturally occurring manufacture or composition of matter—a product of human ingenuity 'having a distinctive name, character [and] use.'" *Chakrabarty*, 447 U.S. at 309-10.

Accepting the government's view broadly, *see* GBr.24-26, would deprive patent protection needed for development of the next antibiotic, the next useful industrial enzyme from a bacterium, and myriad other useful chemicals. It would vastly reduce the financial viability of developing new therapies and decimate a growing sector of the United States workforce.

B. Congress Determines the Appropriate Scope of Patent Subject Matter Eligibility Under § 101

Notwithstanding the unique social implications of the current case, absent any clear and certain signal from Congress, this Court should not disrupt the widely accepted application of the patent laws and § 101.[19] *See* 61-62a; *see Deepsouth*

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[19] A reversal by this Court would upset the current practice of the lower courts, the PTO, and the biotechnology industry. Such a reversal would also place U.S. common law in dissonance with international standards. *See, e.g.*, EU Directive 98/44/EC (implemented by the European Patent

Packing Co. v. Laitram Corp., 406 U.S. 518, 531 (1972); *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 28 (1997). It is not up to the judiciary to narrow the "wide scope" Congress envisioned for § 101 or upset the long-standing practice of the PTO, which has "specific expertise in issues of patent law," and is charged with the task of examining and issuing patents. *Bilski*, 130 S. Ct. at 3225 (quoting *Chakrabarty*, 447 U.S. at 308); *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 145 (2001); *Microsoft Corp. v. i4i Ltd.*, 131 S. Ct. 2238, 2242 (2011). Rather, Congress, beholden and answerable to the public, is best equipped to balance the policy considerations here at issue. *See Charkrabarty*, 447 U.S. at 303, 309, 317-18; PBr.54-55 ("It is not for the Court to balance policy considerations . . . ."). "Given the complicated technology and conflicting incentives at issue here, any change must come from Congress." *See* 94a (Moore, J., concurring), 57a.

Congress has recognized the significance and uniqueness of DNA-based patents.[20] It has often

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Convention and indicating that a nucleic acid corresponding to a gene may constitute a patentable invention if isolated from the human body or otherwise synthesized); *Cancer Voices Australia & Anor (ABN 93 322 703 42y) v Myriad Genetics Inc. & Ors.* [2013] NSD 643 (Austl.), *available at* http://www.austlii.edu.au/au/cases/cth/FCA/2013/65.html. (affirming the Australian court's position that isolated genetic material is patentable subject matter).

[20] *See* 92-94a (Moore, J., concurring)(indicating Congress has "explicitly declined to implement legislation to 'affect any of those current existing patents [on human genes]'" and that "it

provided special carve-outs to balance the public interest involving DNA-based inventions. The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act), for example, carved out an exception to the safe harbor for inventions "primarily manufactured using recombinant DNA, [or] recombinant RNA," and set special conditions for the patent extension of an application for a product primarily using recombinant DNA technology. *See* 35 U.S.C. §§ 271(e)(1); 156(a)(5)(B). Section 271(g) established a specific cause of action for infringement where a foreign manufacturer uses a patented "process of preparing a DNA molecule comprising a specific genetic sequence," uses the DNA to make an unpatented protein outside the United States, and then sells the protein in the United States. *See Bio-Tech. Gen. Corp. v. Genentech, Inc.*, 80 F.3d 1553, 1561 (Fed. Cir. 1996)(citing the Senate Report for the Process Patent Amendments Act of 1988). And more recently Congress created an abbreviated approval pathway for biologic products that are "biosimilar" to approved reference products, i.e. derived by recombinant DNA or controlled gene expression methods. *See* Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, §§ 7001–7003.

As a further example, Congress considered DNA-related inventions when it addressed surgical method patents. *See* 35 U.S.C. § 287(c). The bill originally sought to preclude certain surgical

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appears Congress also believes DNA is patentable")(citing the Congressional Record).

procedures from patentability. *See* Gerald J. Mossinghoff, *Remedies Under Patents on Medical and Surgical Procedures*, 78 J. Pat. & Trademark Off. Soc'y 789, 789-801 (1996). As amended and enacted, however, the law balanced the interests of health care practitioners, the biotech industry, and the PTO. While the law ultimately limited infringement liability, it did not change patentability standards. In fact, Congressman Ganske reassured the PTO and industry groups that under the amendment, "[a]ll presently patentable new drugs will remain patentable," and clarified that the law "does not prohibit patents on gene therapy or other similar procedures." 104 Cong. Rec. H8277 (daily ed. July 24, 1996).

Contrary to the assertions of petitioners and the government, Congress is aware of this case, and is already addressing certain issues raised in this appeal. *Compare* 57a, *with* PBr.55, *and* GBr.28-29. Congress recently directed the PTO to "conduct a study on effective ways to provide independent, confirming genetic diagnostic test activity where gene patents and exclusive licensing for primary genetic diagnostic tests exist," which directly responds to the "second opinion issue" raised by petitioners. PBr.8, 45. *See* Leahy-Smith America Invents Act ("AIA"), Pub. L. 112-29, 125 Stat. 338-39 at § 27 (Sept. 16, 2011).[21] The study is currently ongoing. In August 2012, after multiple public hearings and period for public comment, the Department of Commerce indicated "*the complexity and diversity of the opinions, comments and suggestions provided by interested parties, and the important policy considerations involved*," necessitated further review, discussion, and analysis before a final report could be submitted to Congress. *See* 77 Fed. Reg. 71,171 (Nov. 29, 2012)(emphasis added).

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[21] In the original amendment to the Bill, Representative Deborah Wasserman Schultz (D-FL), a breast cancer survivor, proposed a safe harbor for patent infringement for providers of second opinion genetic testing. *See* 157 Cong. Rec. H4433 (daily ed. June 22, 2011).

Accordingly, the PTO and Congress together are currently assessing at least one of the issues petitioners raise.[22] This Court, therefore, should not divest their efforts to assess these complex patent issues that implicate conflicting policies and diverse interests. *See Gottschalk v. Benson*, 409 U.S. 63, 72-73 (1972)(indicating § 101 raises issues that "only committees of Congress can manage, for broad powers of investigation are needed, including hearings which canvass the wide variety of views which those operating in this field entertain"); *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S.Ct. 1289, 1305 (2012)("[W]e must hesitate before departing from established general legal rules lest a new protective rule that seems to suit the needs of one field produce unforeseen results in another. And we must recognize the role of Congress in crafting more finely tailored rules where necessary.").

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[22] Notably in § 33 of the AIA, Congress also addressed 35 U.S.C. § 101, demarcating a line for what constitutes patentable subject matter vis-à-vis a human being: "Notwithstanding any other provision of law, no patent may issue on a claim directed to or encompassing a human organism." During debates over the provision, Congress specifically considered the application of § 33 to DNA-based inventions. *See* 157 Cong. Rec. E1177–80 (daily ed. June 23, 2011)(Rep. Lamar Smith)(listing the types of subject matter § 33 does not apply to).

C. The PTO Position Is Legally Correct

It has been argued that that the PTO position has "been substantially undermined by the position the government has taken in this case." 118a; *see also* GBr.26-30; PBr.53-55. It is problematic, however, that the government agency with greatest scientific and patent law expertise, the PTO, did not participate in the briefing. The government theory on this important patent question was apparently developed with no public comment. This raises doubts as to the degree of deference that should be given to the "government position," especially in view of the apparent scientific and legal errors in the government's brief. *See* Section I, *supra*.

Although petitioners and the government argue that the Court is not *bound legally* by the earlier PTO position, the PTO is the agency with great expertise in science and patent law, and as such deserves—and often receives—great deference on issues of policy through judicial notice. While the MPEP and Examiner Guidelines "are not binding on this [C]ourt," they "may be given judicial notice to the extent they do not conflict with the statute." *In re Fisher*, 421 F.3d 1365, 1372 (Fed. Cir. 2005)(citations omitted); *see also* 117a (Bryson, J., dissenting). The PTO position that isolated DNA molecules are patent eligible should be adopted because it is based on a correct interpretation of the law, and because those policies have succeeded in fostering growth of the pharmaceutical and biological industries. The biologics industry has, from humble beginnings, grown to a $52 billion industry, with the addition of recombinant technology. John R. Thomas, Cong. Research Serv., RL33901, Follow-On Biologics: Intellectual Property and Innovation Issues 1 (2009).

As Judge Moore correctly observed:

> [P]urifying or isolating natural products has historically been exactly the kind of discovery protected by the patent statutes. There is a century-long history of affirming patent protection for isolated and purified biological products ranging from hormones to vitamins to proteins to antibiotics. These inventions must have seemed miraculous at the time, providing previously unknown therapeutic options to treat sickness. The fact that these molecules might have existed in nature did not foreclose patent protection in view of the extraordinary benefits accessible to man after isolation.

94-95a (concurring). The Court should not "destroy long settled industry expectations for no reason other than a gut feeling that DNA is too close to nature to be patentable, an arbitrary decision based on a judge-made exception." 95a.

CONCLUSION

Petitioners seek radical changes in the law for the patenting of biotechnology inventions, based on unique circumstances, erroneous scientific assumptions, and irrelevant legal arguments. Some allegations of the consequences of Myriad's claims are controversial and unproven. The government's attempt at a compromise by excluding patents on all natural molecules would have even broader deleterious effects to the development of biotechnology, medicine, and many other fields.

Developing better diagnostics and treatments could be harmed if patenting of molecules found in nature or man-made molecules related to them (such as isolated DNA) is prohibited based on flawed factual and legal premises.

AMICUS
CURIAE
BRIEF

RECORD
AND
BRIEFS

No. 12-398

FILED
MAR 14 2013
OFFICE OF THE CLERK

IN THE

Supreme Court of the United States

ASSOCIATION FOR MOLECULAR
PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

**ON WRIT OF CERTIORARI TO THE UNITED STATES
COURT OF APPEALS FOR THE FEDERAL CIRCUIT**

BRIEF OF *AMICI CURIAE* UNIVERSITY OF BALTIMORE/JOHNS HOPKINS UNIVERSITY CENTER FOR MEDICINE & LAW, AND LAW PROFESSORS GREGORY DOLIN, M.D., *ET AL.* IN SUPPORT OF RESPONDENTS

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STATEMENT OF INTEREST OF *AMICI CURIAE*[1]

Amicus curiae University of Baltimore School of Law/ Johns Hopkins School of Medicine Center for Medicine & Law is a joint venture between the two universities dedicated to research in the areas of health care law, pharmaceutical and medical technology innovation, increased patient access to health care, and improved understanding of medical technology by the public.

Professor Gregory Dolin, M.D., Co-Director Center for Medicine and Law, University of Baltimore School of Law, Johns Hopkins University School of Medicine, Professor Adam Mossoff, Senior Scholar & Co-Director of Academic Programs, Center for the Protection of Intellectual Property, George Mason University and Professor Mark F. Schultz, Southern Illinois University School of Law, Senior Scholar & Co-Director of Academic Programs, Center for the Protection of Intellectual Property, George Mason University School of Law are *amici curiae* law professors teach patent law and have published peer-reviewed articles in several law reviews discussing patent eligibility of inventions under Section 101 of the Patent Act, particularly as it relates to genetic materials.

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[1] No counsel for a party authored this brief in whole or in part and no party of counsel for a party made a monetary contribution intended to fund the preparation or submission of this brief. No persons other than *amici curiae* or their counsel made a monetary contribution to its preparation or submission. The parties have all either filed blanket waivers with the Court or have explicitly consented to the filing of this brief.

All *amici* are exceptionally familiar with both patent laws and the underlying science, and have an interest that the Patent Act be applied properly, pursuant to the prescriptions of Congress and this Court, and consistent with the underlying scientific principles.

SUMMARY OF ARGUMENT

Genetic medicine is among the most active and promising areas of scientific research. Laboratory synthesized strands of DNA—derived yet distinct from naturally occurring DNA—play a central role in this research, as well as in the commercial diagnostic and therapeutic tools that it generates.

These synthetic DNA strands differ from their natural counterparts in several significant ways: The synthetic strands are not found directly in nature, but rather are constructed or isolated using inventive laboratory techniques. The synthetic strands are smaller, isolated, and focused, while natural DNA incorporates massive genomic information unrelated to a specific gene, mutation, or disease. The synthetic strands possess unique molecular structures and chemical properties unlike anything found in nature. Perhaps most importantly, the synthetic strands provide useful functionality that their natural counterparts lack, specifically in the critical areas of diagnosis and therapy.

Petitioners contend that these synthetic strands are nevertheless mere discoveries latent in natural DNA rather than new inventions eligible for patent protection. Such an assertion misstates both the applicable law and the underlying facts.

From a factual perspective, the differences between natural and synthetic DNA strands are manifest. An inventive step that works from a natural beginning to craft a new item, possessing some similarities to its natural parent but with different forms and properties, distinguishes invention from discovery. There is no place in nature to which one could turn to find an object identical to the claimed inventions—or an object that functions in an identical manner.

From a legal perspective, this Court has long interpreted Section 101 of the Patent Act to define patent-eligible subject matter broadly; anything "made by man" should qualify. Given that the claimed inventions cannot be found anywhere in nature, the analysis should be straightforward. In fact, ample precedent, including this Court's most recent interpretations of Section 101, supports the conclusion that concrete inventions—such as the synthetic DNA strands that the Respondents claim—are patentable, while abstract ideas are not.

Petitioners and their *amici* also rely on public policy arguments against patenting genetic materials. Yet few if any of those purported policy concerns differ from those raised in objection to therapeutic inventions of all sorts. Congress has heard these arguments many times since the first genetic patent was issued more than thirty years ago, and rejected all such entreaties. In that time, Congress has incorporated numerous new rules and limitations on biologic and therapeutic patents—but never the broad, sweeping prohibition that Petitioners now seek.

Congressional policy favoring the patentability of genes is neither capricious nor mistaken. The entire *raison d'être* of the patent system is the promotion of science and the useful arts. Every patent granted, like any grant of exclusive rights, imposes costs on those seeking to use inventions already invented. We bear those costs willingly because we have concluded that the costs are outweighed by the benefits stemming from the fruits of increased inventive activity. Genetic research is hardly an exception. The difficulty in devising useful inventions like those at issue here, coupled with the ease of copying genetic products once invented, argue strongly in favor of patent protection.

Petitioners have asked this court to overrule the Federal Circuit's ruling that synthetic DNA strands are patentable subject matter. We urge this Court instead to follow scientific fact, legal precedent, public policy, and Congressional judgment by affirming the Federal Circuit.

ARGUMENT

I. Isolated DNA Sequences and cDNA are Different from Native, Naturally Occurring DNA.

The patents at issue here are directed to new and distinct chemical entities that are not present in nature. The overall chemical structure, and often the very sequence of the DNA subunits in the claimed products, differs radically from anything that occurs in nature. Never before has Congress or this Court concluded that a new, man-made chemical entity is not patentable subject matter.

A. Human Genes in Their Native State are Chemically Bound to Other Genes and Proteins, Giving them Particular and Unique Chemical and Physical Properties

A DNA molecule consists of two strands of a repetitive sugar-phosphate chain called deoxyribose. *See* BRUCE ALBERTS ET. AL., MOLECULAR BIOLOGY OF THE CELL 98 (3rd ed. 1994). Each strand is a long, unbranched polymer composed of four types of subunits: bases known as adenine, cytosine, guanine, and thymine ("A," "C," "G," and "T," respectively) leading to a structure resembling four kinds of beads strung on a necklace. *Id.* Each adenine base on one strand is paired with a thymine base on the other, and each cytosine base is paired with a guanine base, generating strands that are complementary, not identical. *Id.* at 99. The DNA molecule can be visualized as a zipper with each strand serving as tape and the A, C, T, G base pairs forming the teeth. Unlike a regular zipper, though, a molecule of DNA is neither straight nor flat. Instead, in its "native" state (i.e., the state it assumes naturally inside a living organism) the DNA molecule is twisted into a spiral ladder shape, giving rise to the famous "double-helix" model. *Id.*

Each DNA molecule is packaged in a separate chromosome. *Id.* at 337. The DNA is associated with chromosomal proteins (such as histones) that pack the DNA molecule in an orderly way to protect it from damage and to regulate gene expression. *Id.* at 342; Rajesh C. Rao, *Alternatives to Embryonic Stem Cells and Cloning: A Brief Scientific Overview*, 9 YALE J. HEALTH POL'Y L. & ETHICS 603, 605 (2009). Each chromosome is thus far more complex than a long, twisted ladder; it is a three-dimensional structure of coiled and packed DNA.

Each chromosome contains numerous genes, and the full set of an organism's chromosomes carries the entirety of its genetic information—its "genome." Because the human genome contains upwards of 20,000 genes but only twenty-three pairs of chromosomes, each chromosome must contain hundreds or thousands of genes. *See* Erik Lillquist & Charles A. Sullivan, *The Law and Genetics of Racial Profiling in Medicine*, 39 HARV. C.R.-C.L. L. REV. 391, 410 (2004). Although each cell contains its organism's entire genome, not all genes are expressed or "turned on" at all times.[2] ALBERTS, *supra* at 401. In order to allow for such differential gene expression, cells identify which genes to express through various cellular mechanisms like chemical modification of the DNA molecule or protein binding to relevant segments of DNA in order to turn it "on" or "off." *Id.* at 402-04, 449.

The overall chemical and physical properties of native DNA emerge from this combination of factors: the entire sequence of base pairs (rather than a particular isolated fragment); the chemical modification of its nucleotides; the association with proteins such as histones; and the overall packaging into superstructures such as chromosomes. Each of these factors plays a role in defining and controlling native DNA's molecular weight, chemical charge, three dimensional structure, responsiveness to particular chemicals and enzymes, availability of electrons for other chemical reactions, and every other property.

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[2] If all genes were turned on in all cells all of the time, cell differentiation would be impossible. In other words, cells would not be able to differentially develop into liver cells, brain cells, blood cells, skin cells, etc. That they actually do so is the result of certain genes being expressed in certain cells but not in others.

B. Human DNA is a Set of Genetic Instructions for Proteins — The Building Blocks of Life

The "function" of DNA is to provide a set of genetic instructions for the production of other critical molecules: proteins.[3] *See* Gregory Dolin, *Exclusivity Without Patents: The New Frontier of FDA Regulation for Genetic Materials*, 98 IOWA L. J. 1399, ___ (2013), available at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2020112 at *21.

Amino acids are the building blocks of proteins, and DNA codes for amino acids. *Id.* at *21-22. This coding operates by grouping nucleotides together in groups of three. Mathematically, each triad drawn from the set of four nucleotides defines a potentially distinct code, yielding sixty-four distinct possible values, or "codons."[4] *Id.* For reasons not wholly understood, genes have non-coding regions (known as "introns") that are interspersed among coding regions (known as "exons"). ALBERTS, *supra* at 341. Indeed, the majority of the genetic material, consists of the non-coding regions. *Id.*

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[3] Portions of DNA also code for other molecules such as structural RNAs. However, encoding proteins is the primary function of most of the DNA.

[4] Mathematically, four letters, each used alone, would result in just four permutations. If four letters were used two at a time, sixteen permutations are possible. Only if four letters are used three at a time will the number of permutations (sixty-four) exceed twenty. This results in the genetic code being "degenerate" where multiple codons may code for the same amino acid. For example, codons CGT, CGC, CGA, CGG, AGA, and AGG all code for the same amino acid – arginine. At the same time, only a single codon (ATG) codes for amino acid methionine. *Dolin*, supra at *21-22.

Mutations in a codon sequence, which may occur, for example, by adding or deleting a nucleotide or by changing one nucleotide into another, often result in coding an incorrect amino acid, leading to a defective or completely nonfunctional protein. *Id.* at 102-03. Thus, when diagnosing genetic disorders, it is important to compare the subject sequence to both the normal sequence and all known mutations. *Dolin*, *supra* at *23.

Those diagnostic comparisons require a few further definitions and steps. First, recall that DNA's two strands are complements, not mirror images; the complement of an AAA sequence, for example, is TTT. Next, only one of these complementary strands—known as the "sense" strand—codes for amino acids; its complement is known as the "anti-sense" strand. *Id.* at *24. Diagnosis and treatment require identifying the "sense" strand coding a particular protein, a difficult challenge because both strands contain sense and anti-sense regions. *See* ALBERTS, *supra* at 227. Natural cellular mechanisms, working *in vivo*, can differentiate between the sense and anti-sense strands in native DNA that embodies a complete genetic code. *Id.* Laboratory tools and techniques capable of distinguishing sense from anti-sense strands require innovation and inventiveness beyond the use of natural mechanisms.

C. Production and Processing of RNA is an Intermediate Step in Translating the Genetic Code into Protein Structure

The "decryption" of DNA's genetic code into a protein structure occurs in two steps: transcription and translation. For present purposes—namely understanding why the patent claims at issue describe invented, rather than natural, phenomena—transcription is far more significant than translation.

The process begins when the DNA region containing the relevant active gene is "transcribed" into a corresponding RNA molecule. RNA is comprised of nucleotides attached to a single strand of a sugar molecule called ribose (as opposed to the dual strands of deoxyribose in DNA). *Id.* at 60. The transcription from DNA to RNA copies A, C, and G nucleotides directly, while replacing all T (thymine) nucleotides with U (uracil) nucleotides. *Id.* at 104.

In addition to the replacement of Ts with Us, RNA and DNA differ in several other significant ways. Unlike the native DNA strand that contains multiple genes, only some of which are active, an RNA molecule contains only a single active gene. *Id.* at 340. In a similar vein, single-stranded RNA transcribes only sense regions, never anti-sense regions. *Dolin*, *supra* at *26. Also unlike DNA, RNA lacks the bound histones that fold DNA into the complex chromosomal structures. *Id.* RNA does, however, possess several features that native DNA lacks: a special methylated guanine nucleotide known as a "5' cap" on one side of the strand, and a long tail of 100 to 200 adenine nucleotides, known as a "poly-A tail," on the other. *Id.* These structures, which do not code for amino acids, promote the RNA's stability and permit cellular mechanisms to verify that an RNA strand is intact before decoding it to produce proteins. ALBERTS, *supra* at 369-70.

Before that production can begin, however, a further pre-processing step, known as "RNA splicing," removes non-coding introns from the RNA and splices the remaining exons together in an uninterrupted string known as "messenger RNA," or mRNA. *Dolin*, *supra* at *27. That sets the stage for the "translation" step, where cellular mechanisms read the mRNA, one codon at a time, to produce the final protein structure. *See* ALBERTS, *supra* at 232–36.

All told, even though the DNA dictated the critical sequence of nucleotides in the mRNA molecule, the two molecules differ quite significantly. The removal of a majority of the genetic code; the subsequent splicing, the introductions of the 5' cap and the poly-A tail; the substitution of uracil for thymine; and the use of a different sugar all render the resultant mRNA a very different molecule from the DNA from which it was derived.

D. Laboratory Created cDNA Molecules that are Used to Identify and Treat Disease are Structurally Different from Native State DNA and RNA

Though mRNA serves as the template for protein synthesis, scientists typically have little choice but to work with DNA when studying genes because only active genes produce mRNA and, consequently, proteins. An inactive gene coding a dangerous mutation—such as a cancer—will thus be asymptomatic. Because genetic research attempts to identify such dangers *before* they pose an active threat to their host organism, geneticists *must* study the molecules containing all of that organism's genetic information, inactive as well as active. The only molecules possessing that property are DNA. *See Dolin*, *supra* at *27-28.

In order to locate and identify the quiescent gene on a complex DNA molecule packed with thousands of other genes, scientists create "probe" molecules that bind to the region of interest and locate the targeted gene. *Id.* at *28-30. Because DNA contains two complementary strands with each nucleotide sequence binding to its complement, these laboratory-created probes bind to complementary regions of native DNA. The process for creating such probes is well-known: "reverse transcription" of an mRNA molecule creates a copy of an *in vivo* anti-sense DNA strand's coding regions, known as "complementary DNA," or cDNA (because it is complementary to the mRNA template). *See* ALBERTS, *supra* at 300-03.

Nature does not create cDNA; only laboratory scientists do. cDNA is thus a completely man-made molecule. It differs from the templating mRNA molecule in at least three ways, and from native *in vivo* DNA in at least four ways.

A comparison of mRNA and cDNA reveals that: First, the cDNA is not a copy of the mRNA because it is a double-stranded rather than a single stranded molecule. Second, as a DNA molecule, it uses thymine rather than uracil. Third, the sugar backbones of the mRNA and cDNA strands differ; the mRNA's is ribose while the cDNA's is deoxyribose. *See Dolin, supra* at *29-30.

A comparison of native DNA and cDNA reveals that: First, the cDNA has no introns. Second, since the cDNA is a laboratory-produced molecule, it is not subjected to cellular regulation such as chemical modification of various nucleotides. Third, cDNA is not part of a larger structure such as a chromosome. Fourth, because cDNA is complementary to the mRNA, it has a region complementary to the poly-A tail—a region not present in the *in vivo* DNA. *See id.*

In short, *nothing* about cDNA is "naturally occurring." cDNA is a completely artificial construct useful for studying naturally occurring DNA.

E. Laboratory Created and Isolated DNA Molecules Possess Functions that Native State DNA and RNA Lack

Laboratory-synthesized cDNA molecules are useful as probes to identify genes *in vivo*. While the cDNA strand *as a whole* is not complementary to any *in vivo* DNA sequence (i.e., because cDNA lacks introns), the overlap is sufficient for the cDNA to attach itself to, or "hybridize" with, the native DNA. *See id.* at *30. The points of hybridization, in turn, allow scientists to identify the endpoints of each native gene, to excise each gene using specific (and known) enzymes (i.e., create "isolated" DNA), and to employ well-known (and mostly automated) methods to discover the sequence of each gene. *Id.*

The genetic sequence, once discovered, presents multiple opportunities for scientific advancement, most immediately by helping researchers probe, test, and identify genetic predispositions for cancer and other diseases. *See id.* at *31-32. In some cases, medical scientists can go further by generating genetic therapies for diseases thus diagnosed. *Id.* The ability to isolate and to work with "full" genes (i.e., those with introns present) opens new opportunities for working with transgenic animal (i.e., animals with a foreign gene inserted into their native genome) studies and for treatment of certain diseases (though such experimental interventions are currently in their infancy). *Id.* at *32. Finally, knowledge of the genetic sequence of one gene helps advance research into other genes and biological processes. Diseases and other characteristics are often controlled not by a single gene but by a combination of genes working together. *See id.* at *32-33. In these situations, the expression of some genes is directly affected by expression of others. Given the complex nature of genetic expression, scientists need to build upon, and work with, earlier genetic discoveries in order to continue their exploration.

Various opponents of genetic patents have attempted to draw analogies between genetic research and mining to convince the court that the claims at issue are discoveries rather than inventions. *See Ass'n for Molecular Pathology v. USPTO*, 689 F.3d 1303, 1350 (Fed. Cir. 2012) (Bryson, J., concurring in part and dissenting in part). Such analogies are inapt. The chemical and physical properties of a mineral are fixed and do not change when miners extract the mineral from soil or mineralogists extract it further from ore into an isolated form. Electrical conductivity, reactivity to acids or bases, melting points, or reactivity to other metals remain natural constants. By way of contrast, *all of these properties* of isolated DNA and cDNA differ from those of corresponding native DNA.

Taken together then, isolated DNA and cDNA are more than merely new inventions; they are new inventions that serve distinct and important functions unachievable using only elements found in nature. Unlike their natural counterparts, these laboratory-synthesized molecules lack chemical modification of particular nucleotides; do not associate with binding proteins such as histones; are not part of superstructures such as chromosomes; and have molecular weights, charges, and responsiveness to chemicals and enzymes that differ from native DNA. *See id.* at *68. By any reasonable definition, isolated DNA and cDNA are "not nature's handiwork, but [the inventor's] own." *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980).

II. Prior Decisions of this Court Make Clear that Laboratory-Created Chemical Compounds are Patent Eligible

Since at least 1853, this Court has drawn a line between patent-eligible inventions and patent-ineligible discoveries. *See Le Roy v. Tatham*, 55 U.S. 156, 174-175 (1853). However, it has never mattered whether the invention "is produced by chemical agency or combination; or by the application of discoveries or principles in natural philosophy known or unknown before his invention." *O'Reilly v. Morse*, 56 U.S. 62, 119 (1854). Patent eligibility has always meant that the invention was "not nature's handiwork, but [the inventor's] own," *Chakrabarty*, 447 U.S. at 310, and that the patent described it "in a manner so full and exact, that any one skilled in the science to which it appertains, can, by using the means he specifies, without any addition to, or subtraction from them, produce precisely the result he describes." *O'Reilly*, 56 U.S. at 119. Although the Court has excluded from patent eligibility "[t]he laws of nature, physical phenomena, and abstract ideas," 447 U.S. at 309, it has consistently held that an invention that "come[s] from the application of the law of nature to a new and useful end," *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948), is indeed worthy of patent protection under § 101 (and its predecessors). *See Diamond v. Diehr*, 450 U.S. 175, 187-188 (1981).

Part I, *ante*, explained why isolated DNA and cDNA are neither "nature's handiwork" nor "natural phenomena." Rather, they are produced in the laboratory as the "handiwork" of the inventor, through the application of laws of nature, which are taken "from the laboratory of the philosopher, and ma[de] the servant of man." *O'Reilly*, 56 U.S. at 132. As this Court held in *The Telephone Cases*, when "[t]he art consists in so controlling the force [of nature] as to make it accomplish the [inventor's] purpose," the claims to such art are in fact eligible for patent protection. 126 U.S. 1, 532 (1888).

The late Chief Judge Markey once observed "'[o] nly God works from nothing. Men must work with old elements.'" *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 n.3 (Fed. Cir. 1985) (quoting Howard T. Markey, *Why Not the Statute?*, 65 J. PAT. & TRADEMARK OFF. SOC'Y 331, 334 (1983)). That the isolated DNA and cDNA molecules claimed by the Respondents are derived from a naturally occurring substance does not and should not change the analysis. Indeed, in the field of biological and medical science most, if not all, substances are derived and purified from naturally occurring compounds. In fact, as far back as 1873 Louis Pasteur was issued a patent on purified yeast. *See* U.S. Patent No. 141,072. Neither Congress nor this Court have ever viewed such lineage as a reason to deny patent eligibility to the derived products.

A. As a Matter of Science, the Claims in Myriad's Patents are Indistinguishable from Claims in Chakrabarty's Patents

In *Diamond v. Chakrabarty*, Dr. Ananda Chakrabarty sought to patent a known species of bacterium that he endowed with new biological properties. 447 U.S. at 305.

His "inventive process" essentially merged the DNA of one bacterium with the DNA of another. *See* U.S. Patent No. 4,259,444, col. 2, ll. 38-46. As Dr. Chakrabarty explained in his disclosure, both of the merged DNA molecues (known as plasmids) were naturally occurring and well known, as were the bacteria that carried each of the plasmids. *Id.* Furthermore, the methods for inserting foreign plasmids into a new host were also well known in the art by the time Dr. Chakrabarty created his transgenic bacterium. *Id.* at col. 2, ll. 8-28.

Although there was much concern over permitting patents on living organisms, *see Chakrabarty*, 447 U.S. at 316 (describing concerns "that genetic research may pose a serious threat to the human race, ... [that it] may spread pollution and disease, that it may result in a loss of genetic diversity, and that its practice may tend to depreciate the value of human life."), the Court correctly concluded that Congress had consciously crafted the "subject-matter provisions of the patent law ... in broad terms to fulfill the constitutional and statutory goal of promoting 'the Progress of Science and the useful Arts.'" *Id.* at 315. Applying these broad Congressionally-defined contours, the Court concluded that the microorganisms that Dr. Chakrabarty invented are not a "natural phenomenon, but [] a nonnaturally occurring manufacture or composition of matter – a product of human ingenuity 'having a distinctive name, character and use.'" *Id.* at 309-10 (quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887)).

From the scientific perspective though, the key to Dr. Chakrabarty's invention was not the bacterium, but the plasmid – the DNA – that he created in his laboratory and ultimately transfected into the claimed bacterium. *See*

U.S. Patent No. 4,259,444, col. 2, ll. 38-55. The invention worked only because the bacterial DNA coded for enzymes that provided a degradative pathway for a variety of hydrocarbons. *Id.* at col. 3, ll. 5-23. Had Dr. Chakrabarty sought to patent the newly created plasmid (or combination of plasmids), he likely would have achieved the same legal result. This hypothetical patent would have had the same reach as the patent that ultimately issued, and the subject matter of that hypothetical patent would still have been "a product of human ingenuity 'having a distinctive name, character and use,'" even though each component was both known and naturally occurring.

The case at hand cannot be distinguished in a meaningful way. The Respondents claim isolated DNA and cDNA sequences that are capable of hybridizing to native DNA. These sequences have "a distinctive name, character and use" different from sequences that occur in nature. It is these man-made fragments that are useful and used in diagnosing predisposition to breast cancer. In *Chakrabarty*, the invention consisted of inserting two separate known pieces of DNA into a single cell in order to cause that cell to express both genes. U.S. Patent No. 4,259,444, col. 10, ll. 46-52. The case at bar, at the very least with respect to cDNA, is identical. As discussed in Part I, creating cDNAs is a multi-step process that includes excising pieces of DNA from the native sequence and annealing the remaining pieces together. The only difference between this process and the patent eligible process in *Chakrabarty* is that here, all pieces of the DNA come from a single organism, while in *Chakrabarty*, each piece of DNA was sourced from a different organism. This distinction should not be relevant to a determination of patent eligibility of the subject matter; the fundamental inventive process and the ultimate inventive result are the same in both cases.

A similar analysis applies to isolated DNA. Although isolated DNA includes only the process of cutting DNA segments from a larger molecule and does not include re-annealing, the isolated DNA claimed by the Respondents still differs from anything that occurs in nature. Not only does the isolated compound have different chemical and physical properties, it also has a "distinctive … use." Unlike naturally occurring chromosomal DNA, isolated and purified DNA can be used to specifically identify and differentiate normal from mutated *in vivo* DNA sequences. *See Dolin, supra* at *27-33. Because human intervention is required to produce isolated DNA, the isolated DNA is chemically and physically different from naturally occurring DNA. Because that newly-invented isolated DNA has a distinct purpose and uses, it is patent eligible subject matter.

B. Isolated DNA and cDNA are Patent Eligible Under the Principles and Logic of *Parke-Davis*

Courts and commentators have long viewed *Parke-Davis & Co. v. H. K. Mulford Co.*, 189 F. 95 (C.C.S.D.N.Y. 1911), as a clear and correct statement of patentability in the field of biologic arts. In *Parke-Davis*, Judge Hand concluded that adrenaline, extracted from the adrenal gland and purified to be both therapeutically and commercially useful, was "a new thing," not a naturally occurring substance—and thus eligible for patent protection. *Id.* at 103. Though adrenaline is indeed a naturally occurring compound produced by the body's adrenal glands, its medicinal uses emerge only after isolation and purification. *See* Michael D. Davis, *The Patenting of Products of Nature*, 21 RUTGERS COMPUTER & TECH. L.J. 293, 326 (1995). The process of isolation and purification therefore took the naturally occurring product from the state of nature "and ma[de it] the servant of man" by giving it a new utility.

The Fourth Circuit adopted the *Parke-Davis* approach in *Merck & Co. v. Olin Mathieson Chem. Corp.*, 253 F.2d 156 (4th Cir. 1958). There again, the patentee patented an isolated and purified form of a naturally occurring chemical compound – in that case, vitamin B-12. Faced with a challenge to the patent under the "product of nature" doctrine, the Fourth Circuit concluded that the patentee

> has produced a medicine indisputably beneficial to mankind -- something new in a useful art, such as our patent policy was intended to promote. ... And it makes no difference, so far as patentability is concerned, that the medicine thus produced is lifted out of a mass that contained, chemically, the compound [in question] -- where the one is therapeutically available and the others were therapeutically unavailable – patentability would follow."

Id. (quoting *Kuehmsted v. Farbenfabriken of Elberfeld Co.*, 179 F. 701, 705 (7th Cir. 1910)).

What underlies the holdings in *Parke-Davis*, *Merck*, and *Kuehmsted* is the understanding that patent laws exist to "promote the Progress of Science and useful Arts," U.S. Const., Art. I, §8, cl. 8, and that inventions which create new medical therapies do in fact "promote the Progress of Science." That Constitutional utilitarian justification has always underpinned the patent system, *see* Adam Mossoff, *Rethinking the Development of Patents: An Intellectual History*, 1550-1800, 52 HASTINGS L. J. 1255, 1256 n.7 (2001), and its implications should be instructive in any consideration of the proper scope of patent eligibility—including the present one. *See Dolin*, *supra* at *40-46. From the perspective of public policy, the relevant question is thus whether granting patents on genetic compounds isolated and purified from their natural state to make them diagnostically and therapeutically useful would spur innovation in excess of the costs implicit in any grant of exclusive rights. *See id.* at *78-79. Given the extraordinarily high capital cost and the inherent uncertainty of genetic research, compounded by the negligible cost of copying new discoveries, the answer should be clear. The patent system is necessary to motivate scientific research and to protect the commercially viable discoveries emerging from the research laboratories. *See id.* at *91.

C. *Prometheus* and *Funk Brothers* are Not to the Contrary

This Court's own precedents, at the very least from *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948) through the more recent *Mayo Collaborative Services v. Prometheus, Inc.*, 566 U.S. ___, 132 S. Ct. 1289 (2012), support a holding that isolated and purified DNA and cDNA are patent eligible subject matter.

In *Funk Bros.*, the Court concluded that a particular mixture of bacteria, though useful for agricultural purposes, is not patent eligible subject matter because the claimed invention was "hardly more than an advance in the packaging of the inoculants." 333 U.S. at 131. In the Court's view, the aggregation of bacteria into a single package was "no more than the discovery of some of the handiwork of nature and hence is not patentable."[5] *Id.* The Court's decision ultimately rested on the absence of any inventive step whatsoever. In the view of the Court, the *Funk Bros.* "inventor" did *nothing* to modify the bacteria in the mixture, and the mixture resulted in no individual strains of bacteria acquiring a new "range of their utility. Each species has the same effect it always had. ... Their use in combination does not improve in any way their natural functioning. They serve the ends nature originally provided and act quite independently of any effort of the patentee." *Id.* In contrast, unlike naturally occurring DNA, isolated DNA and cDNA serve important diagnostic and therapeutic purposes, thereby giving these man-made molecules a new "range of utility," making them serve the ends different from what nature originally provided, and causing them to act only because of the "effort of the patentee" who created these particular molecules precisely to allow such therapeutic and diagnostic interventions.

Similarly, in *Prometheus*, the Court concluded that a patent on optimizing the level of a particular drug in a body does not satisfy § 101 requirements because the claim merely embodied the scientific truth that too little of the drug is ineffective, while too much is poisonous. The claimed method in *Prometheus* simply "set forth laws of nature-namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a [the] drug will prove ineffective or cause harm," and directed the treating physician to increase an ineffective or decrease a harmful dosage of the drug. 132 S. Ct. at 1296. In other words, the patents claiming the method of administering the drug did nothing more than recite the method by which the immutable law of nature works. The human involvement in the claimed method was merely a "conventional [and] obvious, ... insignificant post-solution activity." *Id.* at 1298 (internal citations and quotations omitted). The *Prometheus* Court, however, cautioned against "too broad" an application of the principle that "[p]henomena of nature, ... are not patentable," *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972), because such "an interpretation ... could eviscerate patent law. For all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas." 132 S. Ct. at 1293.

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[5] In the view of the *amici*, *Funk Bros.*, was incorrectly decided and should be overruled. However, as described below, the patents at issue in the present case would satisfy even the overly broad "product of nature" exception articulated in *Funk Bros.*

Applying the *Prometheus* principles to the present case, it becomes clear that the invention the Respondents claim is patent eligible subject matter. Extracting DNA from the chromosome, separating coding from non-coding regions, re-annealing these regions, and/or reverse transcribing DNA sequence from an RNA molecule, are neither "conventional [nor] obvious, [nor] insignificant post-solution activit[ies]." Indeed these activities lie at the very heart of molecular and medical genetics research. While no one disputes that all breakthroughs in molecular and medical genetics "embody, use, reflect, rest upon, or apply laws of nature [and] natural phenomena," *the* *results* of this research remain well within the ambit of patent protection. The decision in *Prometheus* did not alter the dichotomy that "'[w]hile a scientific truth, or the mathematical expression of it, is not a patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be,'" *Diamond v. Diehr*, 450 U.S. 175, 188 (1981) (quoting *Mackay Radio & Telegraph Co. v. Radio Corp. of America*, 306 U.S. 86, 94 (1939)), instead re-affirming it. *Prometheus*, 132 S. Ct. at 1294.

The DNA molecules that Respondents claim are not natural phenomena, but rather "novel and useful structure[s] created with the aid of knowledge of scientific truth," *Diehr*, 450 U.S. at 188, and therefore deserving of patent protection. Holding otherwise would expand the scope of the "products of nature" exception to patent eligibility far beyond its original scope and purpose: ensuring that monopolization of scientific principles not impede innovation by foreclosing access to the "basic tools of scientific and technological work." *Gottschalk*, 409 U.S. at 67.

There is no evidence to suggest that patents on man-made genetic materials impede medical research and scientific progress in any way that differs from the effects of other therapeutic patents.[6] Thus, excluding man-made

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[6] As one study has shown, these patents are almost never asserted against an entity using genetic materials as a basic research tool. *See* Christopher M. Holman, *The Impact of Human Gene Patents on Innovation and Access: A Survey of Human Gene Patent Litigation*, 76 UMKC L. Rev. 295, 343 (2007). Indeed the study was able to identify only a single case involving the "actual sale of a cloned human gene *per se* as opposed to the sale

DNA molecules from patent eligibility would accomplish the opposite of what the "products of nature" exception was meant to achieve. Instead of keeping "manifestations of ... nature, free to all men and reserved exclusively to none," *Funk Bros.*, 333 U.S. at 130, denying patent eligibility to man-made DNA molecules would significantly reduce the incentives impelling research medical and molecular genetics research forward, thus delaying the discovery of new and useful diagnostic and therapeutic tools, and retarding, rather than promoting the "progress of science," *see Dolin, supra* at *91, all without any palpable increase in the access to the tools of research. *See* Christopher M. Holman, *The Impact of Human Gene Patents on Innovation and Access: A Survey of Human Gene Patent Litigation*, 76 UMKC L. Rev. 295, 352-61 (2007) (stating that patents on DNA have had no negative impact on research or access to research tools, and may have in fact had positive impact).

III. It is Up to Congress, Not the Courts to Define The Limits of Patentability.

The first application for a patent on genetic materials was filed in 1978 and issued as a patent in 1982. U.S. Patent No. 4,363,877 (filed Apr. 19, 1978) (issued Dec. 14, 1982). Calls immediately arose to deny patents to such applications. *See, e.g.*, Robert P. Merges, *Intellectual Property in Higher Life Forms: The Patent System and Controversial Technologies*, 47 Md. L. Rev. 1051, 1058-60 (1988) (discussing ethical objections to patenting

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of a product incorporating the gene (for example, the transgenic mouse []), or the use of the gene in the production of a product or the performance of a service." *Id.* at 343-44.

genetic materials and living organisms); Rebecca S. Eisenberg, *Proprietary Rights and the Norms of Science in Biotechnology Research*, 97 YALE L.J. 177 (1987) (discussing perceived conflicts between the intellectual property regime and the norms of scientific research). Numerous parties have lobbied Congress to deny patent protection to genetic materials. *See* Joel J. Garris, *The Case for Patenting Medical Procedures*, 22 AM. J. L. AND MED. 85, 107 (1996). In the ensuing decades, individual members of Congress have introduced several bills attempting to limit or to end the patenting of genetic materials; not a single one has progressed beyond the committee stage. *See, e.g.*, H.R. 977, 110th Cong. (2007); H.R. 3967, 107th Cong. (2002); H.R. 977, 110th Cong. (2007); S. 2111, 100th Cong., 2d Sess. (1988); H.R. 3119, 100th Cong., 1st Sess. (1987). The implication is clear: Congress believes that genetic materials are patentable subject matter, and sees little reason to alter that *status quo* in any way. *See Dolin*, *supra* at *71-74.

Congress has amended the Patent Act several times since the issuance of that first genetic patent in 1982—without ever restricting genetic patents. In 1984, for example, Congress amended the Patent Act to declare that "[i]t shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention ... solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." 35 U.S.C. § 271(e)(1). Similarly, in 1996, Congress immunized medical practitioners from charges of infringement resulting from practicing patented medical techniques. 35 U.S.C. § 287(c)(1). Starting in 2004, Congress has on a yearly basis enacted a ban on the use of federal funds "to issue patents on claims directed to or encompassing a human organism." *See* Consolidated Appropriations Act, 2006, Pub. L. No. 109-149, § 509, 119 Stat. 2833, 2880 (2006); Consolidated Appropriations Act, 2005, Pub. L. No. 108-447, § 626, 118 Stat. 2809, 2920 (2005); Consolidated Appropriations Act, 2004, Pub. L. No. 108-199, § 634, 118 Stat. 3, 101 (2004). In 2011, Congress wrote this restriction into the substantive Patent Act. *See* Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 4, 125 Stat. 284, 340 (2011) (amending 35 U.S.C. § 101). In short, over the years, Congress has considered and adopted several mechanisms that limited the scope of the Patent Act either by proscribing the issuance of patents to certain technologies or limiting the ability of patent holders to enforce their patents against a particular class of alleged infringers. Congress, however, consciously chose not to exclude man-made genetic materials from the reach of the Patent Act. *See Dolin, supra* at *71-74.

"Congress, not the courts, must define the limits of patentability." *Chakrabarty*, 447 U.S. at 315. Congress has time and again chosen to define the patent eligible subject matter broadly. As this Court stated just three Terms ago, "Section 101 ... precludes the broad contention that the term[s of § 101] categorically exclude[]" any particular type of inventions. *Bilski v. Kappos*, 561 U.S. ___, ___, 130 S. Ct. 3218, 3228 (2010). As in *Bilski*, "[t]he argument that [human genes] are categorically outside of § 101's scope is further undermined by the fact that federal law explicitly contemplates the existence of at least some [human gene] patents." *Id.* Section 101 of the Patent Act, as recently amended by the Leahy-Smith America Invents Act, currently prohibits issuance of patents "on a claim directed to or encompassing a human organism." 35 U.S.C. § 101(a). If § 101 were construed to categorically exclude patents on human genes from its scope, the limitation added by the Leahy-Smith America Invents Act would have been superfluous, as any patent directed to a human organism would necessarily encompass a patent on genetic material. According such a construction to § 101 "would violate the canon against interpreting any statutory provision in a manner that would render another provision superfluous." *Bilski*, 130 S.Ct at 3228.

The Petitioners' arguments have, thus far, not carried the day in either Congress or the Executive Branch. Nothing prevents them from continuing to press their arguments in those arenas. However, they should not be permitted to use this Court to upset the considered judgment of Congress developed over nearly three decades of debate on the issue, and that of the Executive Branch, which, having considered the argument and concerns raised, has continued to issue patents on man-made genetic materials. *See J.E.M. Ag Supply v. Pioneer Hi-Bred Int'l*, 534 U.S. 124, 144-45 (2001) (concluding that courts should not disturb a long and consistent practice by the USPTO which has been acquiesced in by Congress). As this Court has itself recognized, it is

> without competence to entertain these arguments -- either to brush them aside as fantasies generated by fear of the unknown, or to act on them. The choice [the Court is] urged to make is a matter of high policy for resolution within the legislative process after the kind of investigation, examination, and study that legislative bodies can provide and courts

> cannot. That process involves the balancing of competing values and interests, which in our democratic system is the business of elected representatives. Whatever their validity, the contentions now pressed on [the Court] should be addressed to the political branches of the Government, the Congress and the Executive, and not to the courts.

Chakrabarty, 447 U.S. at 317 (1980).

IV. The Functionality Standard Relied on by the Petitioners and Some Amici Does not Make Sense in the Context of Biological Medicine.

Petitioners and some *amici* have argued that man-made DNA ought to be ineligible for patent protection because its function does not differ from naturally occurring DNA. *See, e.g.*, Pet. Br. at 34-35; Br. of Fifteen Law Professors at 37-38; Br. of Am. Med. Ass'n, et al., at 24-26. This argument is both incorrect as a factual matter and, if taken to its logical conclusion, nonsensical in the context of biological medicine.

As an initial matter, isolated DNA and cDNA possess important functional capabilities that naturally occurring DNA lacks. While it is true that both the natural and the artificial molecules code for the same amino acid sequence, the functional similarities stop there. The only function of the naturally occurring DNA is to provide a code for the ultimate amino acid sequence, which is derived after the DNA is transcribed and translated. Although isolated DNA and cDNA are also capable of producing proteins (given the proper biological environment), they have functions beyond protein production, and they are used for those functions rather than for protein production: isolated DNA and cDNA serve diagnostic functions by binding to *in vivo* DNA and helping to identify genetic mutations. *See* Part I.C, *supra*.

Furthermore, biological medicine works precisely because the therapeutic agent can simulate the function of a naturally occurring substance, often (as here) in addition to its other functions. For example, laboratory produced insulin is useful only because it serves the same function (and operates in the same manner) as insulin produced by pancreas *in vivo*. Yet, that has never been cause to deny patents for a variety of insulin analogues. For example, the UPSTO issued U.S. Patent No. 5,618,913 was issued in 1997 for insulin aspart (marketed as NovoLog/RapidLog). The insulin analogue described in the patent acts in the exact same manner as naturally produced insulin does, and is indeed chemically identical to naturally occurring insulin but for modification in the single amino acid. See FDA, NovoLog Insulin Aspart Label, available at http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4254b_13_04_KP%20InsulinAspartFDAlabel102005.pdf.[7] Despite these similarities in structure and identity of function, there has never been any question that these insulin molecules satisfy § 101 of the Patent Act. Similarly, low molecular weight heparin (an anti-coagulant) has the same function as naturally occurring heparin that is produced by mast cells. Yet U.S. Patent No. 4,990,502 (issued Feb. 5, 1991) protects it. ("Low molecular weight heparins of regular structure, their preparation and their biological uses.").[8]

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[7] Other patents have issued on similar insulin analogues. *See, e.g.*, U.S. Patent No. 5,750,497 (covering insulin determir, which differs from naturally occurring insulin by a single amino acid); U.S. Patent No. 5,656,722 (covering insulin glargine, which differs from the naturally occurring insulin by just three amino acids).

Adopting the Petitioners' and *amici*'s functionality analysis would eviscerate an entire field of scientific and medical exploration. By categorically denying patent protection to the fruits of such research, the Court would seriously undermine the incentives to engage in this painstaking and extraordinarily expensive endeavor. Such an approach would privilege chemical-based medical treatments (with all the attendant side-effects) over biological ones (which replace the naturally occurring substance that, due to disease, is not produced in sufficient quantities). Under the Petitioners' view, the traditional chemical drugs would continue to be patent eligible because the particular chemical would have no naturally occurring counter-part, while the biological therapeutic agent modeled on the agent produced *in vivo* would not be patent eligible. Given the evolution of medicine towards biologic treatments, such a result would be not only anomalous, but highly detrimental to the "progress of science" and to improvements in medical therapeutics.

V. Any Questions About Novelty and Scope of Prior Art Must be Answered by Applying Sections 102 and 103 of the Patent Act.

Petitioners and some *amici* argue that the claims to isolated DNA and cDNA lack an "inventive step" that transforms a "product of nature" into patent eligible subject matter. *See, e.g.*, Pet. Br. at 35-39; Br. of Nat'l Women's Health Network, et al., at 29-30; Br. of Academics in Law, Medicine, Health Policy and Clinical Genetics at 25-31. This argument confuses and conflates separate requirements of the Patent Act into a single inquiry under § 101.

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[8] A number of other patents covering variations of heparin have been issued as well.

Judge Giles Rich – one of the crafters of the Patent Act of 1952 – described the system thus:

> Achieving the ultimate goal of a patent under those statutory provisions involves, to use an analogy, having the separate keys to open in succession the three doors of sections 101, 102, and 103, the last two guarding the public interest by assuring that patents are not granted which would take from the public that which it already enjoys (matters already within its knowledge whether in actual use or not) or potentially enjoys by reason of obviousness from knowledge which it already has.
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> ...
>
> The first door which must be opened on the difficult path to patentability is § 101 (augmented by the § 100 definitions) ... whether [the] invention is patentable or not.
>
> ...
>
> If the invention, as the inventor defines it in his claims ... falls into any one of the named categories, he is allowed to pass through to the

> second door, which is § 102; "novelty and loss of right to patent" is the sign on it.
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> The third door, under the 1952 Act, is § 103 . . . .
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> . . .
>
> Section 103 ... refers to the difference between the subject matter sought to be patented and the prior art, meaning what was known before as described in section 102. If this difference is such that the subject matter as a whole would have been obvious at the time [the invention was made] to a person [ordinarily] skilled in the art, then the subject matter cannot be patented.
>
> If the inventor holds the three different keys to the three doors, his invention (here assumed to be "useful") qualifies for a patent, otherwise not.

In re Bergy, 596 F.2d 952, 960-62 (C.C.P.A. 1979). Thus, the issue of whether the patentee was sufficiently inventive or merely made a conventional and obvious change or improvement is not to be analyzed under § 101, but rather under § 103.

It may well be that as knowledge and skill in molecular and medical genetics evolve, some genetic discoveries will fail § 103 analyses. *See generally Dolin*, *supra* at *83-91. As the Federal Circuit recognized in *In re Kubin*, "an obviousness finding [is] appropriate where the prior art 'contain[s] detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.'" 561 F.3d 1351 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 902 (Fed. Cir. 1988)). As the art of molecular genetics continues to evolve and the methodology for isolating and purifying DNA and for creating cDNA becomes more "detailed" and "enabling," the evidence that modification of prior art "would be successful" will become stronger and stronger, and the granting of exclusive patent rights will become more and more limited. *See Dolin, supra* at *83-91.

Petitioners, however, have chosen not to challenge Respondents' patents on the grounds of obviousness;[9] instead, they have chosen to import the obviousness inquiry into the § 101 patent eligibility analysis. This approach is contrary to well-established principles of patent law and to the intent of Congress that, in 1952, specifically separated the patent eligibility and obviousness inquiries into the different sections of the Patent Act. The Court should not entertain the Petitioners' attempt to rewrite the Patent Act and conflate what should be separate inquiries into a single issue.

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[9] The *amici* express no view on the issue of obviousness with respect to Respondents' patents.

CONCLUSION

The Federal Circuit correctly held isolated DNA and cDNA to be patent-eligible subject matter and should be affirmed.

Respectfully submitted,

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AMICUS
CURIAE
BRIEF

Supreme Court, U.S.
FILED
[illegible]
OFFICE OF THE CLERK

No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF JAMES D. WATSON, PH.D. AS *AMICUS CURIAE* IN SUPPORT OF NEITHER PARTY

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INTEREST OF *AMICI CURIAE*[1]

Amicus curiae James D. Watson, Ph.D., is the co-discoverer of the double helix structure of deoxyribonucleic acid ("DNA"). For this discovery, he and his colleague, the late Francis Crick (along with the late Maurice Wilkins for related work), were awarded the Nobel Prize in Physiology or Medicine in 1962. *See* James D. Watson, *The Double Helix* (1968).

Throughout his career, Dr. Watson has been at the forefront of recombinant DNA research and advances in genetic engineering. From 1956 until 1976, Dr. Watson was on the faculty of Harvard University, leading the effort to focus the biology department on the then-emerging field of molecular biology. Starting in 1968, Dr. Watson was the director of Cold Spring Harbor Laboratory ("CSHL"). From 1994 to 2004, he served as the president of CSHL, and from 2004 until 2007, he was CSHL's Chancellor. Dr. Watson is now Chancellor Emeritus of CSHL.

Dr. Watson's current research relates to the causes and potential cures of cancers. His interest in cancer first publicly expressed itself through his teaching on tumor viruses after he joined the Harvard University Biology Department in the fall of 1956. At that early stage, his lectures explored how cancer might be induced by DNA tumor viruses, the smallest of which probably had DNA sufficient to code for only 3–5 proteins. His expertise with recombinant DNA and cancer research lends particular insight into the case at hand, which concerns the patentability of human genes relating to breast cancer.

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[1] The petitioners have filed a letter of blanket consent to *amici* on January 2, 2013. Respondents granted consent to *amicus* on January 9, 2013, via electronic mail, a copy of which is being submitted herewith. *Amicus* and his counsel represent that no party to this case nor their counsel authored this brief in whole or in part, and that no person other than *amicus* paid for or made a monetary contribution toward the preparation and submission of this brief.

The author of numerous books and research articles, Dr. Watson has received several honors for his scientific research, including the Albert Lasker Prize (1960), the Nobel Prize in Physiology or Medicine (1962), the John J. Carty Gold Medal of the National Academy of Sciences (1971), the Presidential Medal of Freedom (1977), the Copley Medal of the British Royal Society (1993), the Lomonosov Medal, Russian Academy of Sciences (1995), the National Medal of Science awarded by the National Science Foundation (1997), the University of Chicago Medal (1998), the New York Academy of Medicine Award (1999), the University College London Prize (2000), the Benjamin Franklin Medal for Distinguished Achievement in the Sciences (2001), and an Honorary Knighthood of the British Empire (2002).

Of particular relevance to the question presented to the Court is Dr. Watson's role in the Human Genome Project and his career-long involvement with recombinant DNA research. Dr. Watson was one of the earliest proponents of sequencing the human genome. In 1988, Dr. Watson was appointed Associate Director for Human Genome Research at the National Institutes of Health ("NIH") and, in 1989, Director of the National Center for Human Genome Research at the NIH. In these positions, Dr. Watson initiated and led the public effort to sequence the human genome. Even at that time, the question of whether human genes should be patented was one of critical importance.

Given the importance of the question presented, Dr. Watson presents his arguments from his personal, unique perspective on the issue of whether human genes are patentable.

* * *

SUMMARY OF THE ARGUMENT

Human genes should not be patented. *First*, a human gene is fundamentally unique—unlike any ordinary "composition of matter." A gene conveys information—the instructions for life. As a product of nature, a human gene's primary purpose is to encode the information for creating proteins, enzymes, cells, and all the other components that make us who we are. I explained much of this when I submitted my amicus brief to the appeals court, but that court was unpersuaded. So I reiterate what I told the appeals court: Life's instructions ought not be controlled by legal monopolies created at the whim of Congress or the courts.

Second, much of what we now know about human genes traces back to the Human Genome Project, which was structured as a public works project, intended to benefit everyone by deciphering our genetic code. Our goal was to construct a map of what already existed in nature, namely our genes. Accordingly, I, along with other prominent scientists, expressed the strong opinion that human genes should not be patented. There was simply no need for it. Others, including some at the National Institutes of Health, disagreed. Eventually, much but not all of the human genome was dedicated to the public through the efforts of the Human Genome Project. It was a mistake by the Patent Office to issue patents on human genes and a mistake by those who filed for those patents.

Third, human gene patents are not necessary to encourage scientists to advance our knowledge and develop innovative new medicines or biotechnology inventions. The important innovations needing patent protection are not the human genes themselves but the technologies that use human genes. And here, it is important that the human genes can be reasonably accessible so that as many top minds as possible can develop the new technologies based on the human genes. As you read this, scientists are creating new procedures using hundreds, if not thousands, of genes for diagnosing and treating life-threatening diseases, including breast cancer. Innovation will be rewarded based on those developments, not the patenting of the human gene. Thus, if it were decided that human genes can be patented, courts should grant compulsory licenses. Such licenses would ensure access to human genomic information on reasonable terms, guaranteeing that our genomic map creates the most benefit for mankind.

ARGUMENT

I. Because Human Genes Are Unique And Convey Information About The Essence of Being Human, They Should Not Be Patented

I have read through the various opinions issued in this case.[2] The opinions admirably describe the scientific details of DNA and human genes, but the opinions by the appeals court miss the fundamentally unique nature of the human gene. Simply put, no other molecule can store the information necessary to create and propagate human life the way human DNA does. It is a chemical entity, but DNA's importance flows from its ability to encode and transmit the instructions for creating a human being.

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[2] I have also read the Supreme Court's decision in *Mayo v. Prometheus*, although its opaqueness must leave many attorneys wondering if it adds anything at all to the issue of whether human genes ought to be patented.

The question presented to this Court is one which, I believe, requires an appreciation of the history of human DNA research. The appeals court appeared not to fully appreciate this history and how it necessarily informs the inquiry. Moreover, Congress has not enacted any specific law which says that human genes are patentable. Indeed, the nature of the gene—and the double-helical structure of DNA on which genes are encoded—mandate that a human gene does not fall within the ordinary meaning of "composition," as Congress set forth in the 1952 Patent Act.

Even before DNA's structure was revealed, many scientists recognized the importance of a cell's chromosomes (which are composed of DNA) to the propagation of life. In 1944, Erwin Schrödinger, a Nobel Prize-winning physicist, wrote a small book titled *What Is Life?* In it, he reasoned that chromosomes were the genetic information bearers. Schrödinger thought that, because so much information must be packed into every cell, the information must be compressed into "hereditary code-script" embedded in the molecular fabric of the chromosomes. The same year, Oswald Avery, Maclyn McCarty, and Colin MacLeod provided empirical proof that DNA was the genetic material. Even so, many skeptical scientists questioned this finding, until 1952, when Alfred Hershey and Martha Chase laid to rest any doubts with their experiments done at Cold Spring Harbor Laboratory.

The secret to DNA's ability to create life is its double helical structure, along with its information-coding sequences. Francis Crick and I published the first correct structure of DNA in 1953. J.D. Watson & F.H.C. Crick, *A Structure for Deoxyribose Nucleic Acid*, 171 Nature 737 (1953). Building on the X-ray crystallographic work of Maurice Wilkins and Rosalind Franklin, Francis and I determined that DNA forms a double helix. At the time, we were in a tight race with Linus Pauling (soon to be a Nobel laureate in chemistry and later a laureate for the Peace Prize). Fortunately for us, Pauling concluded that DNA was a triple helix—an erroneous conclusion ironically based on a chemical error made by a most-brilliant chemist.

The double-helical structure of DNA epitomizes elegance in simplicity. From a chemical perspective, DNA is a simple compound, little more than two strands of a nucleotide polymer wound together in a double-helix formation. The nucleotide polymer consists of various sequences of A, T, G, and C bases. The two strands of the double helix are complementary to each other.[3]

When Francis and I deciphered the structure, we immediately understood its significance. With a hint of more to come, we wrote in our article that "[i]t has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material." *Id.* The double-helix structure confirmed DNA's role as the genetic carrier and created the possibility of almost limitless information storage. The various sequences of bases could be translated by a cell's machinery, and that information would be used to create new proteins for the cell. Following physicist George Gamow's suggestion, Sydney Brenner and Francis Crick later demonstrated that the smallest informational unit, the codon, was three bases long, *e.g.*, AAA, TTT, etc.

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[3] Amusingly, after I gave my first presentation of our DNA structure in June 1953, Leó Szilárd, the Hungarian physicist and an inventor of the nuclear chain reaction, asked whether I would patent the structure. That, of course, was out of the question.

Later scientists discovered that certain DNA sequences controlled the expression of other genes. One of the earliest of these control sequences discovered was the "TATA box." The TATA box contains the core DNA sequence 5'-TATAAA-3' or a similar variant. Specific proteins can bind to this sequence, which promotes the transcription of other specific genes. Extracted from the chromosome, a nucleic acid molecule having the TATAAA sequence has little, physically inherent value. Its significance arises because that sequence is useful information to the cell's genetic machinery. The TATAAA sequence leads to the expression of genes that affect the cell and ultimately our human experience.

The terminology of molecular genetics underscores DNA's informational role in life. In a living cell, DNA is used to make RNA, and then RNA is used to make polypeptides, *i.e.*, protein. The first step—DNA to RNA—is called "transcription." The second step—RNA to proteins—is called "translation." Both words connote the conveyance of information instead of simply the creation of new chemical entities, and for good reason. The information encoded by a human gene is first *transcribed* into RNA (DNA and RNA are similar molecules, thus similar languages, so the genetic information is merely transcribed from one format to another). Then, the genetic information is *translated* from RNA into protein. (RNA and protein are different biochemical "languages," hence translation). The entirety of the DNA machinery relates to transferring and utilizing the genetic information.

When cells replicate, they make copies of the genetic code for the progeny cells. New strands of DNA are synthesized in a process analogous to the way scriveners of years past would copy legal documents. Just as scriveners would copy legal documents word by word, a cell copies the DNA molecule letter by letter (A, T, G, or C). And just as scriveners proofread their work, the DNA polymerase—the enzyme that replicates DNA—has a built-in proofreading mechanism. But as with all proofreading, the system is not perfect, and errors occur. "Typographical" errors with DNA replication can lead to genetic mutations—which can cause devastating diseases or can lead to evolutionary improvements.

To this day, we continue to learn how human genes function. We estimate that humans have approximately 21,000 genes. We have yet to fully understand the functions of all human genes, but this lack of understanding is further reason that scientists should be permitted to experiment on human genes free from any threat of patent infringement.

The social history of human genes also reveals the unique informational component of human DNA that sets it apart from other chemical compounds. In the early part of the twentieth century, many in society believed that the answers to all of society's ills resided in the human genome. From that belief grew the ill-fated eugenics movement, founded on an incomplete understanding of human genetics.

Even the esteemed Justice Oliver Wendell Holmes, along with some of his colleagues, misunderstood the role of genes in human development. In the landmark case of *Buck v. Bell*, 274 U.S. 200, 207 (1927), Justice Holmes expressed a view about genetics that prevailed during his time:

> It is better for all the world, if instead of waiting to execute degenerate offspring for crime, or to let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind. . . . Three generations of imbeciles are enough.

We now know that many factors affect a person's mental acuity, genes being some of them. But Justice Holmes and other supporters of the eugenics movement could not appreciate, at that time, the precise role of how genetics determines and influences a person.

In years to come, with the right advances in genetic engineering, we may well be able to treat or rectify mental disabilities and physical diseases which today are deemed incurable. Such hope is all the more reason that scientific research on human genes should not be impeded by the existence of unnecessary patents. More importantly, we would not want one individual or company to monopolize the legal right to the beneficial information of a human gene—information that should be used for the betterment of the human race as a whole.

By the 1970s, the public's perception of DNA and genetic technology had reached its nadir. Far from being viewed as the vindicator of the wrongfully accused—as the public often sees it today—recombinant DNA technology was considered by many to be inherently dangerous. In fact, various interest groups wanted to ban recombinant DNA research.[4] Ironically, this hysteria seemed to begin after I participated in the first scientific discussions exploring whether proposed regulations on DNA research were necessary (at the Gordon Research Conference of Nucleic Acids in June 1973).

Unfortunately, the initial ruminations mutated into full-fledged proposed restrictions, issued from the Asilomar Conference in February 1974. Later, in the summer of 1976, as the hysteria increased, the National Institutes of Health ("NIH") published guidelines governing recombinant DNA research. Shortly after, the public discourse reached such a fevered pitch that, in the summer of 1976, the Cambridge City Council declared a three-month moratorium on all recombinant DNA research in the city of Cambridge—and therefore at Harvard University and the Massachusetts Institute of Technology. These decisions had significant consequences, in some cases forcing scientists to abandon and discard the results of their experimental research.

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[4] I recount much of this history in one of my books. *See* James D. Watson & John Tooze, *The DNA Story: A Documentary History of Gene Cloning* (1981). Another good article is Michael Rogers, *The Pandora's Box Congress*, Rolling Stone, June 19, 1975, at 36, which is reprinted in *The DNA Story*.

Congress also joined the bandwagon of trying to regulate recombinant DNA research. In the fall of 1976, the late Senator Edward Kennedy, as chair of the Senate Health Subcommittee, conducted hearings on whether Congress should enact legislation restricting recombinant DNA research. Some in Congress even wanted to ban the research.

I, of course, did not favor these restrictions. I explained at the time that "our Congressmen are being asked to decide between two silly alternatives." J.D. Watson, *In Defense of DNA*, The New Republic, June 25, 1977, at 11. At one point, I had to defend recombinant DNA research from the attacks of the actor Robert Redford, who, along with the Environmental Defense Fund, raised money hoping to halt basic research experiments using recombinant DNA. *See* James D. Watson, *The Nobelist vs. The Film Star: DNA Restrictions Attacked*, Washington Post, May 14, 1978, at D1. Other prominent scientists, including but not limited to Joshua Lederberg and Stanley Cohen, were vocal in their defense of recombinant DNA research. Eventually, reason and objectivity prevailed, NIH loosened its guidelines, and Congress refrained from enacting detrimental legislation. Scientists were again free to conduct their recombinant DNA research without absurd restrictions.

My point with this overly brief and incomplete history of the early days of recombinant DNA research is to illustrate how those major controversies associated with human genes arose because human genes are much more than chemical compounds. The myopic perspective thinks of a human gene as merely another chemical compound—another composition—consisting of various bases and sugars wrapped together in a double helix. Science and history teach us otherwise, however.

During the height of the hysteria, a popular columnist for the San Francisco Chronicle asked, "Why will scientists persist in playing God?" *See* James D. Watson & John Tooze, *The DNA Story: A Documentary History of Gene Cloning* 165 (1981) (reprinting Charles McCabe, *On Playing God*, San Francisco Chronicle, Apr. 4, 1977). We were not playing God, but that is what many people thought—not because of who we were but because we were working with the instructions for creating human life.

Human genes—quintessential products of nature—are useful because they convey vital information. The human genome's ability to be our instruction book on life distinguishes human DNA from all other chemicals covered by the patent laws. No other molecule carries the information to instruct a human zygote to become a boy or a girl, a blonde or brunette, an Asian, African, or Caucasian.

Some may suggest that all the above has little relevance to whether human genes are patentable. But that suggestion ignores the important social consequences of restricting the use of human genes. Our history confirms that a human gene is not just another chemical compound. A human gene is a product of nature and is more than simply a fragment of a longer DNA polymer. A human gene's patentability cannot depend simply on whether a covalent bond is broken during purification. Human genes—unlike any other chemical composition—reveal information that can be important in life-or-death situations. The information contained in our genes lets us predict our future. With a gene sequence in hand, we can know with some degree of certainty whether we will develop cancer, a neurological disease, or some other malady. This information should not be monopolized by any one individual, company, or government.

II. The Human Genome Project Was Intended To Benefit All, Not Just Select Companies

In addition to understanding the uniqueness of human DNA, an awareness of the Human Genome Project's history should guide the Court to the correct decision that human genes, as products of nature, should not be patented. The Human Genome Project was started not to increase the profits of select companies but to expand our understanding of the human genome and make this information available to all scientists. To permit patent monopolies on human genes would contravene the spirit of the multinational, taxpayer-subsidized, public works effort to sequence the human genome.

The genesis of the Human Genome Project dates to the mid-1980s, when the dual technological advances of recombinant DNA and computers opened the door to deciphering the human genome. In June 1986, I organized a special session at Cold Spring Harbor Laboratory to discuss the beginnings of what would become the Human Genome Project. At that time, the U.S. Department of Energy had also begun to focus on sequencing the genome. Other eminent scientists joined the early effort, including but certainly not limited to Bruce Alberts, Sydney Brenner, and David Botstein. Eventually, we published our report (from the National Academy of Sciences) making the case for sequencing the human genome. With the support of James Wyngaarden, then-head of NIH, and many others, the Human Genome Project became a reality.

In May 1988, I was appointed Associate Director for Human Genome Research of NIH (and later, in 1989, became NIH's Director of the National Center for Human Genome Research). In these positions, my role was to oversee a multimillion-dollar budget and to organize what had become a multi-agency, international effort to decipher the human genome. The United States directed the project and carried out half of the work, while the rest was done mainly in the United Kingdom, France, Germany, and Japan.

Even at the early stages of the project, we were concerned about the issue of patenting human genes. Most, although not all, eminent scientists recognized that human genes should not be monopolized by patents. I believed at the time—and continue to believe—that the issue of patenting human genes went to the very crux of whether the information encoded by human DNA should be freely available to the scientific community and the public at large. Some twenty years ago, I explained that patenting human genes was lunacy, and I was not a lone voice.

Sadly, and to the detriment of scientific research, my view did not control the policy decisions of NIH, which had filed for numerous patents covering human genes. Even more egregious were the types of patents being filed on human genes. Many of NIH's patents described only small fragments of genes and other unknown sequences of the human genome. In June 1991, an NIH official had urged Craig Venter, who at the time was working at NIH, to file patent applications on several hundred new DNA sequences, even though, in many instances, neither Venter nor NIH had any inkling of what those sequences did. The following year, Venter listed over 2,000 more sequences in his patent applications, still having no clue about the function of those sequences. It was preposterous to grant patents on genes, fragments of genes, random bits of human DNA, and who knows what else when the scientists themselves had no clue as to what the DNA sequences did.

I expressed my objections to NIH management, but to no avail. To me, it was clear that the purpose of the Human Genome Project was to map and publish the human genome sequence for the scientific community. It was not to provide raw data to individual companies seeking government-backed exclusivity on the genetic code. As the then-leader of the project, I felt a particular obligation to do what I could. In my view,

> [t]he Human Genome Project is much more than a vast roll call of As, Ts, Gs, and Cs: it is as precious a body of knowledge as humankind will ever acquire, with a potential to speak to our most basic philosophical questions about human nature, for purposes of good and mischief alike.

James D. Watson, *DNA: The Secret of Life* 172 (2003). In 1992, I publicly opposed NIH's decision to patent human genes. As a result, I was left with no choice and therefore resigned from NIH that year.

By that time, the Project was well underway, and I felt comfortable that my departure would not have a negative effect. Notably, patenting human genes was not necessary to complete the Human Genome Project. Indeed, the international effort was proceeding on schedule without any need to file patent applications on human genes. Fortunately, my successor, Francis Collins, had the good sense to understand that gene patenting was not necessary and inhibited fundamental research. He later explained that "[t]he information contained in our shared instruction book is so fundamental, and requires so much further research to understand its utility, that patenting it at the earliest stage is like putting up a whole lot of unnecessary toll booths on the road to discovery." Francis Collins, *The Language of Life: DNA and the Revolution in Personalized Medicine* (2010).

Less than fifteen years after its start, the Human Genome Project, along with Celera Genomics, achieved success. On June 26, 2000, President Bill Clinton and Prime Minister Tony Blair announced that the two groups had finished a working draft, which was published for the public in February 2001. Gaps in the rough draft were filled in by 2003—fifty years after Crick and I published the structure of DNA. Scientists have used the data to estimate that humans have approximately 21,000 genes—in some sense a surprisingly small number compared to other organisms.

The Human Genome Project was a multi-agency, international effort. It was funded in large part by taxpayer money, and the primary expectation was that the information derived from the sequenced human genes would be available for all scientists to use. Unfortunately, a decade later, private companies are still trying to unnecessarily restrict access to human genes and the information encoded in those genes. This situation burdens all of society. Other scientists involved in the Human Genome Project continue to warn about the harms caused by patenting human genes. John Sulston, who received the 2002 Nobel Prize in Physiology or Medicine, headed the British effort of the Human Genome Project. He has explained that "many human genes have patent rights on them and this is going to get in the way of treatment unless you have a lot of money." *See* Alok Jha, *Human Genome Project Leader Warns Against Attempts to Patent Genes*, The Guardian, June 24, 2010, at http://www.guardian.co.uk/science/2010/jun/24/human-genome-project-patent-genes.

Fortunately, much of the human genome was placed in the public domain. The Human Genome Project made efforts to ensure that gene sequences were published as soon as possible. The publication of the sequence limited the number of patents on human genes. Nonetheless, private entities, the NIH, and other entities have obtained patents on some of these genes. Eventually, the problem will disappear, as those patents expire. But in the interim, the Court should rule that human genes, as products of nature, are not patentable.

III. Human Gene Patents Are Not Necessary, But If They Are Granted, Compulsory Licenses Should Be Granted To Ensure Fair Access

In general, lawyers and judges misunderstand scientific research when they contend that patent protection is necessary to encourage scientists to discover human genes. A scientist does not—and should not—expect to obtain a legal monopoly over the information encoded by human genes. And the average scientist should not expect a windfall simply for revealing the sequence of DNA bases that encode various genes. Research on human genes is one of those rare endeavors which should be—and is—done with the understanding that, although inventions based on those genes may later be commercialized, the genes themselves are to be employed for the maximum benefit of humankind.

Consider also whether a biotechnology or pharmaceutical company derives major revenue from the sales of human genes. From what I have seen, the answer is generally no. Most biotechnology and pharmaceutical companies do not derive much, if any, revenue from selling or licensing human genes. Rather, their primary revenue comes from products and services, such as pharmaceutical drugs or research tools, that might be based on human genes. The Court should not be overly concerned that banning patents on human genes will cause a detrimental loss of revenue.

Patenting human genes also deters and obstructs advances in genetic technologies that require the use and evaluation of multiple genes. For instance, investigators at the University of Washington have developed parallel gene sequencing methods for identifying inherited mutations in breast and ovarian cancer genes. *See* Tom Walsh, et al., *Detection of Inherited Mutations for Breast and Ovarian Cancer Using Genomic Capture and Massively Parallel Sequencing*, 107 Proceedings of the National Academy of Science USA 12,629 (2010). This group's approach uses multiple genes, not just the specific BRCA1 and BRCA2 genes in the Myriad patents, to estimate cancer risk.

My own recent investigations have highlighted the complicated genetic basis of human diseases. For instance, complete genome sequencing is advancing our understanding of complex neurological diseases, such as schizophrenia, autism, Alzheimer's disease, and Parkinson's disease, to name just a few. *See* Huda Akil, et al., *The Future of Psychiatric Research: Genomes and Neural Circuits*, 372 Science 1580 (2010). It is becoming increasingly clear that the etiology of many neurological diseases will encompass multiple human genes, acting in concert.

Cancer research is also becoming increasingly dependent on a better understanding of the genetic mechanisms underlying the root causes of cancer. *See* Jim Watson, *Oxidants, Antioxidants and the Current Incurability of Metastatic Cancers*, 2013 Open Biology 120144 (Jan. 9, 2013). Specifically, it is imperative that "RNAi methodologies" be employed to identify the remaining major molecular targets for future anticancer drug development.

A human genome cluttered with no trespassing signs granted by the Patent Office inhibits scientific progress, particularly the development of useful tests and medicines in areas requiring multiple human genes. The resources devoted to cancer research, neurological diseases, and other areas will be diverted to concerns about whether one can use a particular human gene. For a new assay using hundreds of human genes, the sea of patents and patent applications would create hundreds, if not thousands, of individual obstacles to developing and commercializing the assay. The best way, in my view, to resolve this problem is to eliminate the unnecessary patenting of human genes.

If, for some reason, patents on human genes are deemed necessary, the next best, albeit imperfect, solution is to require those patent holders to license the patents to other researchers so that scientific progress is not obstructed. This is often called a "compulsory license." In my view, a compulsory license can establish reasonable access to human genes and genetic information—which is what scientists in general want, had the lawyers and courts not complicated matters. Reasonable access facilitates scientific and social progress.

Compulsory licensing would ensure that scientists and the public will have reasonable access to human genes and genetic information. Compulsory licensing will attenuate the negative consequences of the genetic monopolies created by patents. Implementing a compulsory license protocol will also reduce the risk that a patient is denied access to life-saving medicines and technologies using human genes and the information encoded in the genes.

Companies and inventors should not fear the prospect of compulsory licensing of human gene patents. The inventors and investors would continue to receive an appropriate return on their inventions and investments. The upside will be that more researchers will have meaningful access to the essential tools for investigating and understanding the human genome. Best of all, compulsory licensing will diminish the frightening possibility that patients cannot get a second medical opinion. No patient should be subjected to single-source diagnostic testing of a potentially life-altering genetic condition. When viable alternative, gene-based diagnostics exist, a patent should not preclude the availability of those alternatives.

Finally, I do not suggest that all patents relating to recombinant DNA technology should be abolished or denied. Scientists have developed many new and useful innovations based on recombinant DNA technology. In the 1970s, Herbert Boyer and Stanley Cohen started Genentech based on their pioneering work with recombinant DNA. Since then, countless companies have come and gone, advancing the state of the art for recombinant DNA and adding to the storehouse of knowledge along the way. Indeed, this Court itself has recognized that a genetically engineered bacterium—a man-made invention using recombinant DNA technology—can be a patentable invention. *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

Scientists and companies will certainly continue their innovative efforts in the areas of personalized medicine, genome sequencing, recombinant DNA, and related areas. Before too long, it will cost less than $100 to sequence an individual's entire genome. Low-cost sequencing is set to revolutionize entire sectors of medical treatment. Scientists and inventors will continue to be rewarded for their innovations based on human genes. But governments have an obligation to ensure that these scientific advances are not thwarted or delayed by ill-informed policies restricting the use of the genes themselves.

Looking past the four words of the question presented, the ultimate inquiry is what decision will best promote scientific research on human genetics and medicine. That, after all, is what the Constitution requires when it authorizes patents that promote the progress of the "useful arts." U.S. Const. art. I, § 8, cl. 8. Indeed, as I have written before, "[g]ood patents, I would suggest, strike a balance: they recognize and reward innovative work and protect it from being ripped off, but they also make new technology available to do the most good."

James D. Watson, *DNA: The Secret of Life* 122 (2003). And when all is considered, patents on human genes are not good patents.

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CONCLUSION

For the foregoing reasons, Dr. Watson respectfully submits that the Court should hold that human genes are a product of nature and therefore the information encoded by those genes cannot be monopolized by any single entity.

Respectfully submitted,

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